Xenotransplantation and High Tumorigenicity of Feline Tumors in SCID Mice

Kohji MARUO, Tsuyoshi SUGIMOTO, Kaoru SUZUKI, Kinji SHIROTA\(^1\), Hiroyasu EJIMA\(^2\), and Tatsuji NOMURA\(^3\)

Department of Veterinary Surgery, Faculty of Agriculture, Tokyo University of Agriculture and Technology, 3-5-8 Saiwai-cho, Funabashi, Chiba 278, \(^1\)Department of Veterinary Pathology, Azabu University School of Veterinary Medicine, 1-17-71 Fuchinobe, Sagamihara, Kanagawa 229, \(^2\)Department of Veterinary Surgery, Nippon Veterinary and Animal Science University, 1-7-1 Komyo-cho, Masashino, Tokyo 180, and \(^3\)Central Institute for Experimental Animals, 1430 Nagowa, Miyamae-ku, Kawasaki, Kanagawa 213, Japan

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ABSTRACT. Nine feline tumors resected at surgery were subcutaneously xenotransplanted into SCID mice. The primary take rate of the benign and malignant tumors was 50% (1/2) and 100% (7/7) respectively. Six of the eight primary tumor xenografts transplanted and grown in the first recipient were successfully transplanted serially. One feline mammary adenocarcinoma xenograft metastasized to the lung of a SCID mouse. The primary take rate of feline tumors to SCID mice was high and the established xenografts appear to be valuable tools for investigating growth and metastasis mechanisms, and various therapies for feline neoplasms. — KEY WORDS: feline tumor, SCID mouse, xenotransplantation.

Feline cancers, as well as canine cancers, have been becoming one of the major diseases seen in companion animal clinics. Although the incidence of feline tumors is less than half that of canine tumors [8], the rate of malignancy in all feline cases is markedly high [2], and we know that, with humans and dogs, advanced cancers in patient cats are almost impossible to control with any treatment. To investigate this problem, an experimental model needs to be established. Allotransplantation into fetal cats is reported as the experimental in vivo model of the feline cancer [10], however, the experimental procedure and animal management are thought to be more complex than those of immunodeficient mouse models. The establishment of several feline cancer cell lines has also been reported [4, 9], but a cell line generally doesn't reflect all the characteristics of the original tumor with heterogeneity, and when compared with a transplanted tumor, there is a marked selection of the cell populations in repeated passages [3]. We have therefore, attempted the transplantation of feline tumors into SCID mice, which have been reported to show higher take and metastatic rates than nude mice [11, 16, 17].

Four- to ten-week-old male and female C.B-17 SCID mice were obtained from the Central Institute for Experimental Animals in Kawasaki. The mice were maintained in a specific pathogen-free condition as described elsewhere [14]. Nine feline tumors resected at surgery were cut into 3 mm cubes and several pieces were subcutaneously transplanted into the right flank of one to three SCID mice under sterile conditions. The sex of the recipient mice was matched with that of the donor cats to not eliminate hormone dependent growth of the tumors. The transplanted mice were observed for more than four months, and when the xenografts reached a nodule of about 3 cm in diameter, they were transferred to other SCID mice in the same way. If tumor growth was not confirmed by the end of the 4-month observation period, the transplant was judged to have been unsuccessful. All the tumor-bearing SCID mice were fully examined for metastasis. The original feline tumors, subcutaneous tumor xenografts and their metastatic lesions in the SCID mice were fixed in 4% paraformaldehyde and embedded in paraffin. Sections, 4 μm in thickness, were stained with hematoxylin and eosin.

Nine tumors, including 2 benign (one lipoma and one basal cell tumor) and 7 malignant ones (two malignant lymphomas and five mammary adenocarcinomas), without chemotherapy at the resection were xenotransplanted (Table 1). The primary take rates of the feline benign and malignant tumors in SCID mice were 50% (1/2) and 100% (7/7) respectively, in total 88.9% (8/9). All 6 primary xenografts tried to transfer were serially transplanted in SCID mice. Five of these 6 tumor xenografts are being maintained by frozen preservation in liquid nitrogen [15], and one benign basal cell tumor xenograft has been maintained by transfer using SCID mice. The transfer intervals in malignant tumor xenografts were 4–6 weeks except for one xenograft (No.7, 12–16 weeks), and that of the only benign tumor xenograft was very long, 24–28 weeks (Table 1). The histological features of all the subcutaneous tumor xenografts, even after serial passage through SCID mice, resembled their original ones (Fig. 1). Metastasis was observed in the lung of SCID mice transplanted only with the xenograft of the mammary adenocarcinoma from donor cat No.7 (Fig. 2). As the original adenocarcinoma also metastasized to the lung of donor cat, the metastasis in SCID mice was judged to be due to characteristics of the tumor cells. The reason for low metastatic incidence (20%) of the mammary cancer xenografts in SCID mice may be due to the ectopic implantation. The orthotopic implantation of human mammary carcinoma cell lines in nude mice is reported to show a metastatic rate higher than those of subcutaneous implants [13].

There are no reports about xenotransplantation of feline tumors into SCID mice. The primary take rates of malignant tumors from various species in SCID mice are reported as being 53.1% (17/32) for canine tumors [14], and 36.9% (55/149) for human tumors [16]. The take rate of feline malignant tumors in nude mice is also reported as being 60% (3/5) [7]. Our result of the transplantability of feline...
Table 1. The profile of the feline patients with tumors xenotransplanted into SCID mice and their transplantation data

<table>
<thead>
<tr>
<th>No.</th>
<th>Breed</th>
<th>Sex</th>
<th>Age</th>
<th>Primary site</th>
<th>TNM*</th>
<th>Stage*</th>
<th>Histology</th>
<th>Prognosis</th>
<th>Primary take</th>
<th>Transfer interval (w)</th>
<th>Passage No.</th>
<th>Take rate</th>
<th>Meta.</th>
<th>Frozen preservation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mixed</td>
<td>(F)</td>
<td>6Y</td>
<td>Subcutaneous</td>
<td>-</td>
<td>-</td>
<td>Lipoma</td>
<td>Alive (16 mo)</td>
<td>-</td>
<td>24-28</td>
<td>3</td>
<td>7/7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Himalayan</td>
<td>(F)</td>
<td>6Y</td>
<td>Skin</td>
<td>-</td>
<td>-</td>
<td>Benign basal cell tumor</td>
<td>Alive (20 mo)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Mixed</td>
<td>M</td>
<td>9Y</td>
<td>Axillary</td>
<td>-</td>
<td>I</td>
<td>Malignant lymphoma</td>
<td>Recurrence (6.5 mo)</td>
<td>+</td>
<td>6</td>
<td>4</td>
<td>15/15</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Mixed</td>
<td>M</td>
<td>9Y</td>
<td>Axillary</td>
<td>-</td>
<td>II</td>
<td>Malignant lymphoma</td>
<td>Recurrence, dead (5 mo)</td>
<td>+</td>
<td>6</td>
<td>11</td>
<td>28/30</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>Chinchilla</td>
<td>(F)</td>
<td>7Y</td>
<td>Mammary</td>
<td>T2NOMO</td>
<td>II</td>
<td>Adenocarcinoma</td>
<td>Recurrence, alive (24 mo)</td>
<td>+</td>
<td></td>
<td>1</td>
<td>1/1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Siamese</td>
<td>F</td>
<td>13Y</td>
<td>Mammary</td>
<td>T1NOMO</td>
<td>I</td>
<td>Adenocarcinoma</td>
<td>Recurrence, lung meta., alive (12 mo)</td>
<td>+</td>
<td></td>
<td>1</td>
<td>1/1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Mixed</td>
<td>(F)</td>
<td>7Y</td>
<td>Mammary</td>
<td>T2NOMO</td>
<td>III</td>
<td>Adenocarcinoma</td>
<td>Recurrence, lung meta., dead (10 mo)</td>
<td>+</td>
<td>12-16</td>
<td>4</td>
<td>13/13</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>Mixed</td>
<td>F</td>
<td>14Y</td>
<td>Mammary</td>
<td>T2NiaMO</td>
<td>II</td>
<td>Adenocarcinoma</td>
<td>Recurrence, dead (4 mo)</td>
<td>+</td>
<td></td>
<td>4</td>
<td>4</td>
<td>10/10</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>Mixed</td>
<td>(F)</td>
<td>10Y</td>
<td>Mammary</td>
<td>T2NItMO</td>
<td>II</td>
<td>Adenocarcinoma</td>
<td>Recurrence, dead (6 mo)</td>
<td>+</td>
<td>4-6</td>
<td>6</td>
<td>16/16</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

a) Determined by WHO TNM classification of tumors in domestic animals [12].
b) Spayed female cat.
c) Same animal as No. 3.

Fig.1. Feline benign and malignant tumors in the original patients and in SCID mice subcutaneously xenotransplanted. The benign basal cell tumor (No.2) in a feline patient (A) and in a SCID mouse (passage 3, B), HE stain × 262. The mammary adenocarcinoma (No.7) in a feline patient (C) and in a SCID mouse (passage 1, D), HE stain × 131.
malignant tumors in SCID mice cannot be directly compared with that of dogs and humans, however, one of the reasons for the high tumorigenicity of the feline tumors in SCID mice might be due to high malignancy, since the tumor cells recurred in all seven of the malignant cases, with death following within 10 months of the operation in 4 cases (Table 1). Natural murine resistance against the feline tumor might be another reason, deficient natural killer cell sensitivity, or low activity, being another possible cause. The SCID mouse can play an important role as a recipient of benign tumors from cats as well as from dogs [14] and humans [6]. In addition, these tumor xenografts can be used to evaluate the efficacy of chemotherapy and radiotherapy if we take species differences with pharmacokinetics [5] and radiosensitivity, between donor and recipient, into consideration. Tumor xenografts in SCID mice will also allow the evaluation of immunotherapies using the adoptive transfer of immunocompetent cells [1] and the administration of cytokines [18].

Our results have been apparent that SCID mice transplanted with feline tumors showed high tumorigenicity. The established tumor xenografts are expected to be very useful for research into growth and metastasis mechanisms, and development of therapy for feline neoplasms.

REFERENCES