The Effect of Normal Ovarian Tissue on the Ovarian Tumorigenesis in X-Irradiated Mice

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The ovarian tumors induced by X-ray irradiation were histologically examined in ddY/F and C3H/Tw strains of mice 15 months after irradiation. Luteomas were developed predominantly in ddY/F mice after whole-body irradiation and tubular adenomas in C3H/Tw mice. However, when one ovary was shielded from irradiation in ddY/F mice, no ovarian tumors were found in any of the irradiated contralateral ovaries. After the removal of the normal ovary at 1 or 6 months after irradiation, the increase in the incidence of tubular adenomas and the decrease of the luteomas were resulted in ddY/F mice when examined at 15 months after irradiation. No tumors were induced in the ovaries which were grafted subcutaneously after the X-ray irradiation of the recipient. These results suggested that hormonal conditions especially during early stages of tumorigenesis may determine the type of ovarian tumors.

INTRODUCTION

It is generally accepted that the hormonal imbalance is among the important factors for the ovarian tumorigenesis in mice and rats after X-ray irradiation, exposure to chemical carcinogens or surgical manipulations. Hypophysectomy or administration of estrogen completely inhibited the occurrence of ovarian tumors in mice exposed to DMBA or X-rays, although administration of androgen was ineffective.

The presence of a normal ovary also totally abolished the development of tumors in the mouse ovary exposed to X-rays or DMBA.

The present experiments were intended to study whether the inhibitory effect of the presence of a normal ovary on the ovarian tumorigenesis was reversible.

MATERIALS AND METHODS

Female mice of ddY/F and C3H/Tw strains maintained in this laboratory were used in the present study. The animals were irradiated with 130 R of X-ray at 2 weeks of age. A therapeutic type X-ray generator (Toshiba KXC-18) was operated at 25 mA and 180 kVp with 0.5 mm Cu and 0.5 mm Al filters. Dose rate was about
42 R per minute. The ovaries of ddY/F strain of mice exhibit predominantly luteomas after whole-body X-irradiation, whereas those of C3H/Tw strain gave rise to tubular adenomas.¹)

In the first series of experiments, the right ovaries of the ddY/F mice were shielded with a 6 mm-thick lead plate during the irradiation. The shielded right ovaries were removed at various times after the irradiation. In the second series of experiments, the ovaries were exchanged between irradiated mice and non-irradiated mice of the comparable ages 0.5 or 3 months after irradiation in ddY/F and C3H/Tw strains. Only one ovary was transplanted subcutaneously into a concurrently ovariectomized host.

All mice were sacrificed by cervical dislocation 15 months after irradiation. The ovaries were fixed in Bouin's solution. Sections were serially cut at 6 μm and stained with Delafield's haematoxylin and eosin for histological study.

RESULTS

Table 1 shows the effects of the presence of shielded ovaries remaining for various periods of time on the development of tumors in the irradiated counterparts in ddY/F strain of mice (Series 1 experiments). Ovarian tumors developed in 4 of 13 left ovaries in mice given whole-body irradiation. Three luteomas and one tubular adenoma were identified. When the right ovaries were shielded during the irradiation and were kept unremoved until 15 months, no ovarian tumors occurred in any of 6 mice. The irradiated left ovaries were small in size and composed of atretic interstitial tissue and general epithelium (Fig. 1), whereas shielded right ovaries contained oocytes and developing follicles (Fig. 2). If the shielded ovaries were removed 1 day after irradiation, luteomas were developed in 2 of 4 mice. However, when the shielded ovaries were extirpated 1 month later, 6 tubular adenomas and 1 luteoma were found in 7 of 8 mice. When the extirpation were performed 6 months after irradiation, only tubular adenomas occurred in all 4 mice (Fig. 3). All the shielded ovaries

<table>
<thead>
<tr>
<th>Right ovary</th>
<th>Left ovary</th>
<th>Incidence</th>
<th>Type of tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shielded</td>
<td>Extirpated</td>
<td>4/13</td>
<td>3L and 1TA</td>
</tr>
<tr>
<td>Yes 1 day later</td>
<td></td>
<td>2/4</td>
<td>2L</td>
</tr>
<tr>
<td>Yes 1 month later</td>
<td></td>
<td>7/8</td>
<td>1L and 6TA</td>
</tr>
<tr>
<td>Yes 6 months later</td>
<td></td>
<td>4/4</td>
<td>4TA</td>
</tr>
<tr>
<td>Yes No later</td>
<td></td>
<td>0/6</td>
<td></td>
</tr>
</tbody>
</table>

All mice were autopsied at 15 months after irradiation.
L: luteoma, TA: tubular adenoma.
extirpated at 1 or 6 months after irradiation contained follicles of varying sizes and corpora lutea (Fig. 4). Tubular adenomas developed significantly more in mice extirpated at 1 or 6 months than at 1 day (Fisher's exact probability test; P<0.05). Types of ovarian tumors in mice whose non-irradiated ovaries were extirpated on the day following irradiation were significantly different from those in mice extirpated at 1 or 6 months (P<0.05).

The effect of transplantation at various times after irradiation on the development of ovarian tumors was shown in Table 2 (Series 2 experiments). When non-irradiated ovaries in ddY/F and C3H/Tw strains of mice were transplanted subcuta-
neously in the irradiated or non-irradiated mice of the same strain, no tumors have occurred in any of the ovarian grafts when recovered 15 months after irradiation. In contrast, ovarian tumors were found in the irradiated ovaries transplanted in the non-irradiated hosts at 0.5 or 3 months after irradiation in ddY/F strain of mice and at 0.5 months in C3H/Tw females. The type of ovarian tumors in ddY/F strain of mice was exclusively luteoma, and in C3H/Tw strain it was exclusively tubular adenoma.

Table 2
Incidence of tumors in the ovaries subcutaneously transplanted after irradiation

<table>
<thead>
<tr>
<th>Strain</th>
<th>Irradiation</th>
<th>Tumor</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Host</td>
<td>Graft</td>
</tr>
<tr>
<td>ddY/F</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C3H/Tw</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

The ovaries were grafted at 0.5 or 3 months after irradiation. All mice were autopsied at 15 months after irradiation.
+ ; irradiated with 130 R, –; non-irradiated.
L; luteoma, TA; tubular adenoma.

DISCUSSION

Jull reported that granulosa-cell tumors were developed in the DMBA-treated ovarian grafts by 44 weeks even when the recipient mice retained one normal ovary for the first 22 weeks. The present experiments, however, showed that the presence of the non-irradiated ovary had the irreversible inhibitory effect on the luteoma development in ddY/F strain of mice. The potential of luteoma formation has markedly decreased by the presence of the non-irradiated ovary for more than 1 month after irradiation, while the incidence of tubular adenomas has increased.

The occurrence of tubular adenomas may be partly due to the atrophy of the interstitial tissue, because the close relation between the marked downgrowths of the germinal pithelium, the so-called precursor of tubular adenomas, and the atrophy of the interstitial tissue has been observed by the present author. Luteomas were predominantly developed in ddY/F strain of mice and tubular adenomas in C3H/Tw strain when the animals were given whole-body irradiation at 2 weeks of age. The present experiments showed that the procedures of ovarian transplantation itself did not exert any influence on the strain difference in types of ovarian tumors induced by X-ray irradiation and that X-ray irradiation of hosts only had no stimulatory effect on the induction of ovarian tumors.

It was concluded that hormonal conditions especially during early stages of tumorigenesis had a great influence on the incidence and the types of ovarian tumors.
It yet remains to be determined whether the strain difference in the types of ovarian tumors between ddY/F and C3H/Tw strains of mice are due to the differences in hormonal conditions or in genetic factors including oncogenic viruses.19)

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REFERENCES