Paradoxical Effect of Three-Day Thymectomy on Sarcogenesis in the Mouse with Different Dosages of Methylcholanthrene

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ABSTRACT

Past studies have shown that thymectomy in the mouse at 3 days of age but not at birth or after 7 days produces, in later life, a variety of localized autoimmune lesions. In the present work, 3-day thymectomy facilitated subsequent sarcogenesis by low dosages of 3-methylcholanthrene but inhibited oncogenesis by a high dosage. If the presence of autoimmunity implies an increased antitumor immunity, it then follows that increased immunity facilitated low-dose sarcogenesis but inhibited sarcogenesis with a high dose.

INTRODUCTION

It was discovered by Kojima et al. (1) that thymectomy at 3 days of age, but not at birth or after 7 days, engendered in later life a variety of localized autoimmune lesions, thyroiditis, gastritis, oophoritis, etc. These lesions did not occur in sham thymectomized or untreated mice. The particular organ affected and the incidence were determined by the genotype (2). That the lesions were immunological was shown by the fact that disease could be transferred by splenocytes from 3-day thymectomized mice to nude mice (3), to newborn mice (4), or to animals made receptive by thymectomy at birth (5, 6). Furthermore, the lesions were infiltrated with leukocytes, predominantly lymphocytes (6). It was postulated by these investigators that, in order for lesions to occur, the thymus must reside in the mouse until immunoeffector cells had been processed in the thymus and peripheralized; after 3 days of age the thymus would begin to produce suppressors that would prevent clonal expansion of autoreactive effector cells in the periphery, i.e., would prevent autoimmune disease.

Many of the autoimmune lesions were markedly hyperplastic, a feature that was particularly noteworthy in the stomach; the stomach lesions were often easily palpable through the abdominal wall (5). In the case of the ovary, but not as yet in other organs, the lesion occasionally progressed to overt neoplasia (7, 8).

Previous studies of the effects of thymectomy on oncogenesis were undertaken before the critical importance of the exact age at the time of surgery was understood and before it was known that thymectomy at day 3 could produce hyperplastic autoimmune lesions. This fact may account for some of the variations in the results of the past studies of the effects of thymectomy (summary in Ref. 9). In the present study we tested the hypothesis that the increased immune reactivity in the animals that were subject to an increased incidence of autoimmune lesions would facilitate low-dose but inhibit high-dose sarcogenesis.

MATERIALS AND METHODS

The general plan was to compare the tumor incidences in mice that had been thymectomized or sham thymectomized at 3 days of age and then given MCA2 at different dosages. The incidences of various autoimmune diseases were determined histologically (2).

RESULTS

The number of tumors and the number of animals at risk are shown in Table 1. The data of two separate experiments, both of which gave similar results, have been combined.

It is evident that the effect of thymectomy on oncogenesis depended critically upon the strength of the carcinogen stimulus. Three-day thymectomy potentiated the response to the low concentration but inhibited the response to the high concentration (Table 1).

Since the 0.01% MCA resulted in a very low tumor incidence, we decided to investigate the effects of 3-day thymectomy on carcogenesis with 0.1% MCA. This concentration is still too low to be measurably immunosuppressive (11, 12) and the tumor latencies would be quite long. We also took the opportunity to extend the results to another mouse genotype that was known to develop a high incidence of thymectomy-induced autoimmune disease (2). A control group of the same genotype, but not subject to autoimmunity because thymectomy was delayed until the seventh day of life, was also introduced. The results are shown in Table 2; thymectomy at 3 days, but not at 7, potentiated low-dose oncogenesis.

DISCUSSION

Past studies of the effect of thymectomy on hydrocarbon oncogenesis gave rather confusing results; there were reports of potentiation of oncogenesis, but there were also a number of
low autoimmune response to these weakly immunogenic tumors may have been elevated by the 3-day thymectomy to a more
optimal level for tumor growth.

This explanation of the paradoxical effects of 3-day thymectomy is the one suggested by much other current work supporting
the immunofacilitation theory of oncogenesis and it was this theory that inspired the present study (13). The findings
of the present study support the hypothesis that there is an optimal level of host immune capacity for tumor growth, greater
than zero, and reinforce the conclusion, reached by other means, that the optimal level varies inversely with the dosage of carcino-
gen (13).

Whatever the correct explanation of the paradoxical findings of the present study, an exciting implication is that immune
mechanisms apparently play a role in the biology of spontaneous tumors and/or tumors induced by very low levels of
carcinogen. Such tumors are probably better models of most human cancers than are those mouse tumors induced by large
exposure. In the past, the lack of immunogenicity of these tumors and the failure to influence their appearance by immun-
ological manipulations has caused some observers to question whether immune mechanisms play much of a role in human
cancer (17). In the present work, the lowest level of carcinogen was indeed very low, as the low tumor incidence confirmed, but
an immunological manipulation, 3-day thymectomy, was, nevertheless, effective in altering that incidence.

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immunogenicity of tumors induced with two doses of methylcholanthrene.

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for active host defense against cancer, based on personal studies of 27 murine

Table 1  Incidence of tumors at the local site of 5% or 0.01% MCA in C57/H/HeJ
× 129/J F, mice that had been thymectomized or sham thymectomized at day 3
of life

<table>
<thead>
<tr>
<th>T/M*</th>
<th>5% MCA 97 days after MCA</th>
<th>0.01% MCA 400 days after MCA</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Day 3 thymectomy</td>
<td>20/41 49 &lt;0.05 &lt;0.05</td>
<td>9/36 25 &lt;0.1 &lt;0.03</td>
</tr>
<tr>
<td>Day 3 sham</td>
<td>11/14 79</td>
<td>1/17 6</td>
</tr>
</tbody>
</table>

* T/M, number of mice with tumor/number of mice at risk.

Table 2  Incidence of tumors in C57/H/HeJ × 129/J F, mice after 200 days at the
local site of 0.1% MCA in mice that had been thymectomized or sham
thymectomized at day 3 or at day 7 of life

<table>
<thead>
<tr>
<th>T/M*</th>
<th>Day 3 thymectomy</th>
<th>Day 7 thymectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Sham thymectomy</td>
<td>49/69 71 &lt;0.02 &lt;0.001</td>
<td>24/41 59 NS NS</td>
</tr>
<tr>
<td>Thymectomy</td>
<td>37/72 51</td>
<td>18/31 58</td>
</tr>
</tbody>
</table>

* T/M, number of mice with tumor/number of mice at risk; NS, not significant.

* Mann-Whitney U test, one tailed.

* Fisher's exact, one tailed.
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