Short Communication

Induction of colorectal squamous cell carcinomas in rats by dextran sulfate sodium

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Abstract

ACI rats, 15 males and 15 females, were fed a diet containing 1% dextran sulfate sodium for 660 days. Twenty two of 29 surviving rats developed intestinal tumors between 288 and 660 days. Most tumors consisted of papillomas, and 4 squamous cell carcinomas were also induced, in addition to adenomas and adenocarcinomas. No intestinal tumors were observed in rats of the control group.

In a previous paper we reported the carcinogenicity of dextran sulfate sodium, which is a synthetic sulfated polysaccharide composed of dextran with sulfated glucose. Inbred ACI rats fed a diet containing 5% dextran sulfate sodium for 215 days developed intestinal tumors (1). These tumors were induced in the colon and cecum and consisted of adenomas, adenocarcinomas, and papillomas.

Recently, we found that the same strain of rats fed a diet containing 1% dextran sulfate sodium for 660 days developed squamous cell carcinomas, in addition to the tumors observed in the previous experiment. The present report deals with the development of squamous cell carcinoma of the colon and rectum.

Fifteen males and 15 females of inbred strain ACI rats, 1—1.5 months old, were given a diet containing 1% dextran sulfate sodium for 660 days. Dextran sulfate sodium was provided by Meito Sangyo Co., Ltd., Nagoya, Japan; the intrinsic viscosity was 0.08 in 2 M NaCl at 37°C, sulfur content was 18.9%, and weight-average molecular weight was 54 000 (DS-M-1, lot RLS-1075-S). DS-M-1 was mixed with rat basal diet CE-2 (CLEA Japan Inc., Tokyo, Japan) at a level of 1%. The composition of the CE-2 diet is described elsewhere (2). The control group of 10 male and 10 female rats were fed the basal diet without DS-M-1. Water was given ad libitum. The experiment was terminated after 660 days. All animals were autopsied, including ones that died or became moribund as well as rats that survived to the end of the experiment. Tissues were fixed in 10% formalin, sectioned, and stained with H & E.

Of 30 rats fed the 1% DS-M-1 diet, one died 46 days after the start of feeding and the remaining animals survived 288—660 days, as shown in Table I. The average amount of DS-M-1 ingested was 0.15 g/day/rat. All animals fed the 1% DS-M-1 diet showed almost normal stools. However, blood could be seen infrequently on the surface of the stool in the late stage of experiment, i.e., more than 480 days after the start of feeding DS-M-1 diet. The body weight gains of rats fed the 1% DS-M-1 diet were almost the same as those of control rats as shown in Figure 1 and no significant difference was observed between these two groups.

Squamous metaplasia of the colorectal mucosa was found in all animals of the experimental group. Colonic papilloma was first seen in areas of squamous metaplasia in a rat that died 288 days after the start of the DS-M-1 diet as shown in Table I. Intestinal tumors were observed in 22 out of 29 rats or 76% surviving beyond 288 days after the start of the experiment. Most intestinal tumors were induced in the colon and rectum. They were histologically papilloma, squamous cell carcinoma, adenoma and adenocarcinoma. These types of tumor occurred sometimes as multiple intestinal tumors in one and the same animal. Squamous cell carcinomas (Figure 2) were induced in 4 rats and one of them showed a metastasis.

<table>
<thead>
<tr>
<th>Time of death after start of diet (days)</th>
<th>No. of deaths</th>
<th>Intestine</th>
<th>Colon and rectum</th>
<th>Cecum</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
<td>Papilloma</td>
<td>Squamous cell carcinoma</td>
<td>Adenoma</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>46</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>288</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>351—396</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>425—449</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>465—545</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1 b</td>
</tr>
<tr>
<td>640—660</td>
<td>5</td>
<td>13</td>
<td>17</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>15</td>
<td>22</td>
<td>4(M2,F2)</td>
<td>2(F)</td>
</tr>
</tbody>
</table>

*Including rats killed. bTesticular interstitial cell tumor. cTesticular interstitial cell tumor 4, pituitary adenoma 3, adrenal cortical adenoma 3, and urinary bladder carcinoma 2.

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in the mesenteric lymph node. Squamous cell carcinomas were not found in the previous experiment, in which rats received 5% DS-M-1 diet, whereas papillomas were found in a few animals. Such a difference may be attributable to the dietary level and period of administration of DS-M-1.

The incidence of each histological type of intestinal tumor is shown in Table I. In the control group, a pituitary adenoma and testicular interstitial cell tumors were observed in one female rat and 2 male rats, respectively. No intestinal tumors were observed in rats of the control group. Oohashi, et al. (3) reported that the squamous metaplasia of the colorectal mucosa induced by degraded carrageenan progresses irreversibly after the cessation of carrageenan administration. They (3) assumed that the irreversible squamous metaplasia is a precursor of colorectal squamous cell carcinoma induced by degraded carrageenan. The incidence of squamous metaplasia and papilloma of the colorectal mucosa in rats fed 1% DS-M-1 diet was significantly higher than that in rats fed 5% DS-M-1 diet in the previous experiment and colorectal squamous cell carcinoma was induced only in rats fed 1% DS-M-1 diet. These results also suggested that the squamous metaplasia is a precursor of colorectal papilloma or squamous cell carcinoma.

Results obtained in this study revealed that rats fed a diet containing dextran sulfate sodium at low concentration for a long period develop colorectal squamous cell carcinomas, in addition to the adenomas and adenocarcinomas, as seen in rats fed diets containing degraded carrageenan (4,5). Therefore, with regard to its carcinogenicity, dextran sulfate sodium was similar to carrageenan in its target organ and the process of tumor development it elicits. The mechanism of carcinogenesis by sulfated polysaccharides, such as degraded carrageenan or DS-M-1, is still unknown.

Although degraded carrageenan involves a polydisperse material of variable composition that is difficult to obtain and standardize, some of these problems can be avoided by the use of dextran sulfate sodium, a synthetic sulfated polysaccharide. To study the mechanism of carcinogenesis by sulfated polysaccharides, dextran sulfate sodium may be of practical use as an effective material.

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