Strain differences in the susceptibility to azoxymethane and dextran sodium sulfate-induced colon carcinogenesis in mice

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We have recently developed a mouse model for colitis-related colon carcinogenesis by a combined treatment with azoxymethane (AOM) and dextran sodium sulfate (DSS) in male ICR mice. However, strain differences in the sensitivity to AOM/DSS-induced colon carcinogenesis in mice have yet to be elucidated. The aim of this study was to determine the presence of any genetically determined differences in sensitivity to our model of colon carcinogenesis in four inbred strains of mice. Male Balb/c, C3H/HeN, C57BL/6N and DBA/2N mice were given a single intraperitoneal injection of AOM (10 mg/kg body wt), followed by 1% DSS (w/v) in drinking water for 4 days, and thereafter they received no further treatment for up to 16 weeks. At the end of the study (Week 18), all mice were killed and a histopathological analysis of their colon was performed. The incidence of colonic adenocarcinoma was 100% with a multiplicity (no. of tumors/mouse) of 7.7 ± 4.3 in the Balb/c mice and 50% with a multiplicity of 1.0 ± 1.2 in the C57BL/6N mice. On the other hand, only a few colonic adenomas, but no adenocarcinomas, developed in the C3H/HeN mice (29% incidence with a multiplicity of 0.7 ± 1.5) and the DBA/2N mice (20% incidence with a multiplicity of 0.2 ± 0.4). The inflammation and immunohistochemical nitrotyrosine-positivity scores of the mice treated with AOM and DSS in the decreasing order were as follows: C3H/HeN > Balb/c > DBA/2N > C57BL/6N and Balb/c > C57BL/6N > C3H/HeN > DBA/2N, respectively. Our results thus indicated the presence of strain differences in the susceptibility to AOM/DSS-induced colonic tumorigenesis. These differences may have been directly influenced by the response to nitrosation stress due to the inflammation caused by DSS.

Introduction

Colorectal cancer (CRC) is one of the most common malignant neoplasms in both sexes (1). In Western countries, this malignancy is one of the most leading causes of cancer deaths (1). In patients with inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn’s disease, the risk of CRC development is higher than in the general population (2–5). In sporadic and IBD-related CRC, the expression of inducible nitric oxide synthase and cyclooxygenase-2, both of which are associated with inflammation, has been reported to be elevated (6,7). As a result, inflammation is suggested to play an important role in IBD-related CRC (2).

In our recent series of studies on inflammation-related colon carcinogenesis, we developed a novel model of colitis-related colon carcinogenesis using ICR mice. In this animal model, ICR mice received a single dose of a different colonic carcinogen, consisting of either azoxymethane (AOM) (8), 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (9) or 1, 2-dimethylhydrazine (10), followed by a 1-week exposure to 2% dextran sodium sulfate (DSS) in their drinking water, which thus resulted in a high incidence of colonic epithelial malignancy within 20 weeks (8–10). We have previously proposed that the colonic inflammation and nitrosative stress caused by DSS exposure contributes to the development of cryptal dysplasia and neoplasms in the colon (8–10).

AOM is a colonic genotoxic carcinogen that is extensively used for the investigation of large bowel carcinogenesis in rodents (11–13). A synthetic sulfate polysaccharide, DSS, is a non-genotoxic colonic carcinogen that is widely used to produce colitis in rodents, which shares most features with human UC (14–18). It is well known that different strains of mice have different sensitivities to xenobiotic including AOM and DSS (19–28). For example, the Balb/CJ strain is known to be susceptible to AOM (26), whereas, the C3H (29), C57BL/6J (26) and DBA/2 (25) strains are less sensitive to AOM. Regarding the sensitivity to DSS in several mouse strains, Balb/c, C3H/HeJ, and C57BL/6J mice are relatively susceptible to DSS, while DBA/2J mice have been reported to be virtually resistant (27,28). It may therefore be possible that the differences in the genetic background of the mice differently affect the colon carcinogenesis induced by AOM and DSS.

The current study was conducted to determine the different sensitivities to AOM/DSS-induced colon carcinogenesis in four different inbred mouse strains, namely Balb/c, C3H/HeN, C57BL/6N and DBA/2N, by evaluating the incidence and multiplicity of colonic tumors. In addition, an immunohistochemical analysis of nitrotyrosine, a marker of both formation of peroxynitrite (30) and perhaps the inflammation-associated carcino genesis (31), was done to evaluate whether nitrosative stress is involved in the strain difference sensitivity to AOM/DSS-induced colon tumorigenesis.

Materials and methods

Animals, chemicals and diets

For the study 5-week-old male mice of Balb/c, C3H/HeN, C57BL/6N and DBA/2N strains were obtained from Charles River Japan, (Tokyo, Japan). AOM was purchased from the Sigma-Aldrich (St Louis, MO), DSS with a molecular weight of 36,000–50,000 was purchased from ICN Biochemicals,
Cat. No. 160110, Aurora, OH). CRF-1 (Oriental Yeast, Tokyo, Japan) was used as the basal diet throughout the study.

**Experimental procedure**

After they were brought, the mice were acclimated for 1 week with tap water and a pelleted basal diet, CRF-1, ad libitum. The experimental groups in each strain of mice included the AOM and DSS group, the AOM alone group, the DSS alone group and the untreated control group. The experimental protocol in the current study was slightly modified from our original protocol (8). We chose 1% as the dose level of DSS since this dose has been shown to exert sufficient tumor-promoting effects (32). In addition, the duration (4 days) of DSS exposure in drinking water was shortened based on our preliminary investigation, in which 4 days of exposure to DSS was found to enhance AOM-initiated colon carcinogenesis in ICR mice of either sex. All mice were maintained at the Kanazawa Medical University Animal Facility according to the Institutional Animal Care Guidelines, and were maintained under controlled conditions of humidity (50 ± 10%), light (12/12 h light/dark cycle) and temperature (23 ± 2°C).

**Histopathological analysis**

At the end of the experiment (Week 18), all the mice were killed by an ether overdose. At autopsy, their large bowel was flushed with saline and excised. After measuring the length of the large bowel (from the ileocecal junction to the anal verge), it was cut open longitudinally along the main axis and washed with saline. The large bowel was then carefully inspected for the presence of pathological lesions and fixed in 10% buffered formalin for at least 24 h. Paraffin-embedded sections of the large bowel were then made by routine procedures. Any histopathological alterations in the colon were examined on hematoxylin and eosin-stained sections. Colitis was recorded and scored according to the following morphological criteria described by Cooper et al. (33): Grade 0 (Figure 1A), normal colonic mucosa; Grade 1 (Figure 1B), shortening of the basal one-third of the crypts with slight inflammation and edema in the lamina propria; Grade 2 (Figure 1C), loss of the basal two-thirds of the crypts with moderate inflammation in the lamina propria; Grade 3 (Figure 1D), loss of all the crypts with severe inflammation in the lamina propria, but with the surface epithelium still remaining; and Grade 4 (Figure 1E), a loss of all the crypts and surface epithelium with severe inflammation in the mucosa, muscularis propria and submucosa. An exudate containing cell debris, inflammatory cells, fibrin and mucus covers the damaged mucosa.

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![Fig. 1. Various grades of colitis. (A) Normal colon mucosa (Grade 0); (B) shortening the basal one-third of the crypts with slight inflammation and edema in the lamina propria (Grade 1); (C) loss of the basal two-thirds of the crypts with moderate inflammation in the lamina propria (Grade 2); (D) loss of all the crypts with severe inflammation in the lamina propria, but with the surface epithelium still remaining (Grade 3); and (E) a loss of all the crypts and surface epithelium with severe inflammation in the mucosa, muscularis propria and submucosa. An exudate containing cell debris, inflammatory cells, fibrin and mucus covers the damaged mucosa (Grade 4). Hematoxylin and eosin stain. Original magnification, (A–E), 20×.](https://academic.oup.com/carcin/article-abstract/27/1/162/2390964)
of all crypts and the surface epithelium with severe inflammation in the mucosa, muscularis propria and submucosa. Intestinal neoplasms were diagnosed according to the criteria described by Pozharisski (34).

**Immunohistochemistry**

Nitrotyrosine immunohistochemistry was carried out on 4-μm-thick paraffin-embedded sections from the colons in all four strains of mice administered 1% DSS alone as previously described (8,35). The deparaffinized sections were incubated overnight with a primary rabbit polyclonal anti-nitrotyrosine (diluted 1:1500, CHEMICON International, CA) or with a control solution. Control sections included buffer alone or non-specific purified rabbit secondary antibody and avidin–biotin-peroxidase complex (Vectastain Elite ABC kit, Vector Laboratories, Burlingame, CA). The color was developed using 3,3′-diaminobenzidine–4HCl as the chromogen. The stained sections were examined for the localization and intensity of immunoreactivity by microscopy (Olympus AX70, Olympus Optical, Tokyo, Japan). To the degree of nitrotyrosine staining, the following grading scheme (Grade 0–4) was applied: Grade 0, no immunoreactivity and no positive cells; Grade 1, weak immunoreactivity and 10–30% positive cells; Grade 2, mild immunoreactivity and 10–30% positive cells; Grade 3, moderate immunoreactivity and 31–60% positive cells; and Grade 4, strong immunoreactivity and 61–100% positive cells with extensive immunoreactivity (36).

**Statistical analysis**

Where applicable, the data were analyzed using one-way ANOVA with either Bonferroni correction or Fisher’s exact probability test (GraphPad Instat version 3.05, GraphPad Software, San Diego, CA), with P < 0.05 as the criterion of significance.

**Results**

**General observation**

The intake of DSS-containing tap water did not significantly differ among the four strains of mice (data not shown). Mice that received AOM and 1% DSS or 1% DSS alone demonstrated bloody stools either during DSS administration or soon after the cessation of DSS exposure. The degree of this symptom varied among the strains: Balb/c and C3H/HeN mice showed severe symptoms while C57BL/6N and DBA/2N mice showed mild symptoms. The mean body weight and colon length of the mice are summarized in Table I. The mean body weight of the Balb/c mice, which received AOM/DSS, was significantly lower than that of the C3H/HeN mice (P < 0.01) and C57BL/6N mice (P < 0.01), which were given AOM and DSS. A significant difference on the mean body weight was found between the AOM/DSS group and the untreated group (P < 0.001) in Balb/c mice. As listed in Table I, the mean lengths of the colon in the Balb/c mice (P < 0.001) and C3H/HeN mice (P < 0.001) that were treated with AOM/DSS were statistically longer than in the C57BL/6N mice. A significant difference (P < 0.001) was also observed between the C57BL/6N and DBA/2N mice that were exposed to AOM/DSS. The C57BL/6N mice given AOM alone has a significantly shorter colon than the Balb/c (P < 0.01) and DBA/2N mice (P < 0.01) treated with AOM alone. As for the untreated group, the colon length of the C57BL/6N mice was significantly shorter than that of the Balb/c (P < 0.01) and DBA/2N mice (P < 0.01).

**Incidence and multiplicity of large bowel neoplasms**

Macroscopically, colonic neoplasms developed with a different incidence and multiplicity for each strain of mice that received AOM and 1% DSS. Flat, nodular, polypoid or caterpillar-like tumors were mainly located in the middle and/or distal colon if any tumors existed (Figure 2). Histopathologically, they were tubular adenoma (Figure 3A) or adenocarcinoma (Figure 3B). Dysplastic lesions were also observed in the colonic mucosa surrounding the tumors. None of the strains of mice given AOM alone, 1% DSS alone or tap water had any colonic tumors.

The incidence (percent of mice with tumors) of colonic neoplasms is summarized in Figure 4A. The incidence of colonic neoplasms in the Balb/c mice (100%) was significantly higher than in the C3H/HeN mice (29%, P = 0.0034) and the DBA/2N mice (20%, P = 0.0004). A statistically significant difference (P = 0.0115) was also noted between the C57BL/6N (80%) and the DBA/2N mice. The order of the incidence of colonic adenoma was Balb/c mice (90%) > C57BL/6N mice (70%) > C3H/HeN mice (29%) > DBA/2N mice (20%). The incidence of adenoma in Balb/c mice was statistically greater than in C3H/HeN mice (P = 0.0175) and DBA/2N mice (P = 0.0027), and the difference between C57BL/6N mice and DBA/2N mice was statistically significant (P = 0.0349).

The incidence of colonic adenocarcinoma was 100% in the Balb/c mice and 50% in the C57BL/6N mice and a statistically significant difference (P = 0.0163) was found between these two strains of mice. However, this malignancy was not found in the C3H/HeN and DBA/2N mice. As shown in Figure 4B, the multiplicity of colonic neoplasms (/mouse) was 11.4 ± 5.9 in Balb/c mice, 2.2 ± 1.5 in C3H/HeN mice, 2.5 ± 2.1 in C57BL/6N mice and 0.2 ± 0.4 in DBA/2N mice. The value for the Balb/c mice was significantly higher (P < 0.001) than that of other strains of mice. The order of the multiplicity of adenoma was Balb/c mice (3.7 ± 3.3) > C57BL/6N mice (1.5 ± 1.3) > C3H/HeN mice (0.7 ± 1.5) > DBA/2N mice (0.2 ± 0.4). The value for multiplicity of adenoma in the Balb/c mice was statistically greater than in the C3H/HeN

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**Table I.** Body and relative liver weights and lengths of colon in each strain of mice

<table>
<thead>
<tr>
<th>Strain</th>
<th>Treatment (no. of mice examined)</th>
<th>Body weight (g)</th>
<th>Length of colon (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balb/c</td>
<td>AOM—1% DSS (10)</td>
<td>25.1 ± 3.8abc,d</td>
<td>12.7 ± 1.0f</td>
</tr>
<tr>
<td></td>
<td>AOM (4)</td>
<td>30.9 ± 0.8</td>
<td>14.0 ± 1.0f</td>
</tr>
<tr>
<td></td>
<td>1% DSS (5)</td>
<td>34.1 ± 2.0</td>
<td>13.0 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>None (5)</td>
<td>32.4 ± 1.1</td>
<td>13.7 ± 0.55</td>
</tr>
<tr>
<td>C3H/HeN</td>
<td>AOM—1% DSS (7)</td>
<td>30.2 ± 0.6</td>
<td>12.7 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>AOM (5)</td>
<td>32.6 ± 2.2</td>
<td>12.5 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>1% DSS (5)</td>
<td>32.2 ± 1.2</td>
<td>13.1 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>None (3)</td>
<td>31.8 ± 1.1</td>
<td>11.9 ± 0.6</td>
</tr>
<tr>
<td>C57BL/6N</td>
<td>AOM—1% DSS (10)</td>
<td>29.3 ± 1.9</td>
<td>11.1 ± 0.66</td>
</tr>
<tr>
<td></td>
<td>AOM (5)</td>
<td>31.3 ± 2.0</td>
<td>12.8 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>1% DSS (5)</td>
<td>32.0 ± 1.7</td>
<td>11.7 ± 0.55</td>
</tr>
<tr>
<td></td>
<td>None (5)</td>
<td>33.0 ± 4.7</td>
<td>11.6 ± 1.0</td>
</tr>
<tr>
<td>DBA/2N</td>
<td>AOM—1% DSS (10)</td>
<td>28.3 ± 2.3</td>
<td>13.2 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>AOM (5)</td>
<td>28.9 ± 1.3</td>
<td>14.1 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>1% DSS (5)</td>
<td>30.5 ± 0.6</td>
<td>14.0 ± 0.85</td>
</tr>
<tr>
<td></td>
<td>None (5)</td>
<td>30.7 ± 1.4</td>
<td>13.6 ± 1.7</td>
</tr>
</tbody>
</table>

*Mean ± SD.
1Significantly different from untreated Balb/c mice (P < 0.001).
2Significantly different from C3H/HeN mice which received AOM/DSS (P < 0.001).
3Significantly different from C57BL/6N mice which received AOM/DSS (P < 0.001).
4Significantly different from untreated C57BL/6N mice which received AOM/DSS (P > 0.001).
5Significantly different from DBA/2N mice which received AOM alone (P < 0.001).
6Significantly different from untreated DBA/2N mice (P < 0.01).
mice (P < 0.05) and DBA/2N mice (P < 0.01). The multiplicity of adenocarcinoma in the Balb/c mice (7.7 ± 4.3) was the greatest among the four strains and it was significantly larger than that in the C3H/HeN mice (1.0 ± 1.2, P < 0.001).

The scores of inflammation and nitrotyrosine
As shown in Figure 5, the inflammation scores of each strain of mice initiated with AOM and followed by DSS exposure were 1.2 ± 1.1 in Balb/c, 2.3 ± 1.3 in C3H/HeN, 0.4 ± 0.7 in C57BL/6N and 0.6 ± 0.7 in DBA/2N, respectively. The score of C3H/HeN was significantly greater than that for C57BL/6N (P<0.01) and DBA/2N (P<0.01). As for the mice that received 1% DSS alone, the inflammation score of the C3H/HeN mice (1.4 ± 0.5) was the highest among the strains (1.0 ± 1.2 in Balb/c mice and 0.2 ± 0.4 in DBA/2N mice). C57BL/6N mice given 1% DSS alone had quite a low score of inflammation. The mice treated with AOM alone and the untreated mice demonstrated extremely weak inflammation in the colon.

Nitrotyrosine immunoreactivity was mainly observed in the neoplastic cells, cryptal cells, blood endothelial cells and mononuclear cells, which infiltrated the colonic mucosa (Figure 6). The stainability was relatively weak for infiltrative mononuclear cells in comparison with the cryptal cells and endothelial cells (Figure 6). As shown in Figure 7, the nitrotyrosine immunohistochemistry findings for the Balb/c mice (3.6 ± 0.5) treated with AOM and DSS were significantly higher than those for C3H/HeN (1.7 ± 0.8, P<0.001) and DBA/2N mice (1.6 ± 0.5, P<0.001). The score of nitrotyrosine-positivity in C57BL/6N mice (3.4 ± 0.5) was
statistically higher than those in C3H/HeN (P < 0.001) and DBA/2N (P < 0.001) mice. In mice that received 1% DSS alone, the scores in Balb/c (2.8 ± 0.8) and C57BL/6N (2.4 ± 1.1) mice were higher than those in C3H/HeN (1.6 ± 0.5) and DBA/2N mice (1.4 ± 0.5); however, no significant differences were observed among the strains. As for the mice given AOM alone, the scores of nitrotyrosine in the Balb/c mice and C57BL/6N mice were 0.5 ± 0.6 and 0.2 ± 0.4, respectively. C3H/HeN mice and DBA/2N mice treated with AOM alone showed either no or faint stainability of nitrotyrosine. The degree of nitrotyrosine stainability in untreated mice was almost null.

Discussion

The present investigation demonstrated the different susceptibilities of the four strains (Balb/c, C3H/HeN, C57BL/6N and DBA/2N) of mice to colon tumorigenesis induced by the combination treatments with AOM and DSS. Apparently, Balb/c mice were extremely sensitive to AOM/DSS-induced colon carcinogenesis in the present experimental condition. The sensitivity of Balb/c mice observed in the present study was almost similar to those found in ICR mice (8,32,35). Colonic adenocarcinoma also developed in C57BL/6N, but the incidence was lower than in Balb/c. In contrast, the susceptibility of C3H/HeN and DBA/2N to the administration of AOM and DSS was quite low and only a few colonic adenomas developed in both the strains of mice.

Regarding the sensitivity of the mice to AOM initiation, the Balb/CJ mice were reported to have a remarkable susceptibility to the formation of distal colon tumors after treatment with AOM (26), whereas C3H, C57BL/6J, and DBA/2J mice were found to have a low incidence of colonic tumors by AOM initiation (25,26,29). Strain differences in the susceptibility to DSS have also been demonstrated: Balb/c, C3H/HeJ and C57BL/6J are relatively susceptible to DSS, whereas DBA/2J mice are virtually resistant based on the frequency of ulceration or the histological score of inflammation in the colon.
In the current study, the sensitivities of the four strains to DSS were somewhat dissimilar to those of previous studies. The inflammation score of colonic mucosa revealed a severe and moderate inflammation to be present in the C3H/HeN and Balb/c mice treated with both AOM and DSS, respectively, while C57BL/6N and DBA/2N mice had only a relatively weak inflammation. In the case of the receptivity of C57BL mice to lipopolysaccharide (LPS), C57BL/10ScCr mice were resistant to LPS, whereas C57BL/10ScSn mice responded to LPS. Similarly, C3H/HeJ and C3H/HeN are LPS-responder and LPS-non-responder mice, respectively. As a result, the discrepancy in the response of DSS in mice might be due to differences in the substrains. In the current study, the highest incidence of colonic tumors was

(27,28). In the current study, the sensitivities of the four strains to DSS were somewhat dissimilar to those of previous studies (27,28). The inflammation score of colonic mucosa revealed a severe and moderate inflammation to be present in the C3H/HeN and Balb/c mice treated with both AOM and DSS, respectively, while C57BL/6N and DBA/2N mice had only a relatively weak inflammation. In the case of the receptivity of C57BL mice to lipopolysaccharide (LPS), C57BL/10ScCr mice were resistant to LPS, whereas C57BL/10ScSn mice responded to LPS (37). Similarly, C3H/HeJ and C3H/HeN are LPS-responder and LPS-non-responder mice, respectively (38,39). As a result, the discrepancy in the response of DSS in mice might be due to differences in the substrains. In the current study, the highest incidence of colonic tumors was
specific inactivation of the IκBα-b-catenin-accumulated crypts in azoxymethane-induced colon carcinogenesis might correlate with different sensitivities to AOM or DSS, with only slight contradictions among the sub-strains.

AOM is widely used as a colonic carcinogen to investigate the pathogenesis and modification of colon carcinogenesis in rodents (11–13). AOM requires metabolic activation to exert its carcinogenic action. Cytochrome P450 (CYP) is known to play a prominent role in the modulation of the xenobiotic metabolism, including chemical carcinogens. CYP 2E1 is one of the important factors for converting AOM to methyl-azoxymethanol, which can produce DNA adduct formation and also produce the initiation event (40,41). Although we did not investigate the activity of CYP 2E1, it may be possible that the expression and/or content of CYP 2E1 differ among the strains examined. This may be indicated by the findings that the relative liver weight of Balb/c, which had the highest susceptibility of AOM/DSS-induced colon carcinogenesis, was higher than that of other strains of mice in the current study (data not shown). The influence of nitrosation stress caused by DSS is also an important factor for AOM/DSS-induced mouse colon carcinogenesis, since a powerful tumor-promoting activity of DSS has been observed in this model (8,32,35,42). We found a close association between the score of nitrotyrosine and the occurrence of tumors in the current study. Nitrotyrosine-immunohistochemical scores of each strain of mice in the ‘AOM → DSS’ and ‘DSS alone’ groups were much greater than those of the ‘AOM alone’ and ‘untreated’ groups. The scores of the ‘AOM → DSS’ group were relatively higher than those of the ‘DSS alone’ group in all strains of mice and the order was Balb/c > C57BL/6N > C3H/HeN > DBA/2N in these two groups. Such inflammation could influence tumorigenesis, although the inflammation score did not completely correspond with the frequency of colonic tumors in the current study. Indeed, the score of inflammation in the mice receiving both AOM and DSS was higher than that of the mice administered DSS alone. An investigation of additional factors is needed to precisely elucidate the strain differences in the susceptibility to colon carcinogenesis. Recently Greten et al. (43) reported interesting findings, namely that a specific inactivation of the IkB kinase (IKK)/NF-κB pathway can attenuate the formation of inflammation-associated colon tumors in villin-Cre/IκBΔF/3 mice. They also suggested that IκKB might be involved in inflammation-related carcinogenesis.

In conclusion, we herein demonstrated the differences in the genetic susceptibility to AOM/DSS-induced colon tumorigenesis among four inbred strains (Balb/c, C3H/HeN, C57BL/6N and DBA/2N) of mice and found the Balb/c mice to be the most sensitive. Our findings suggest that the genetic background thus plays an important role in the cancer risk in colitis-related colon tumorigenesis. In addition, strain differences in the susceptibility of colon carcinogenesis induced by AOM and DSS might be influenced by the response to nitrosation stress due to inflammation as determined by the genetic background.

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References

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