An Animal Model for the Inflammation-Related Colon Carcinogenesis

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Colorectal cancer (CRC) is one of the most serious complications of inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease. The risk of CRC becomes significant with the extent and duration of the disease. For understanding the pathogenesis of IBD and IBD-related CRC, several animal models were reported. They include a mouse model using dextran sodium sulfate (DSS), but this colitis model needs a long period or cycle administration of DSS to induce colitis and colitis-related CRC. Therefore, we attempted to develop a novel animal model of inflammation-related CRC, in which large bowel adenocarcinomas develop within a short-term period and their histology and biology are resemble to those found in humans. For this, male ICR mice were given a single dose of different genotoxic colonic carcinogens such as azoxymethane (AOM, 10 mg/kg bw), 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP, 200 mg/kg bw), or 1,2-dimethylhydrazine (DMH, 20 mg/kg bw), and followed by one-week oral exposure of 2% DSS in drinking water. Animals thereafter received no further treatment. At wk 20, a high incidence of colonic epithelial neoplasms (adenoma and adenocarcinoma) with dysplasia developed. Immunohistochemistry of dysplasias and neoplasms revealed that these lesions were positive for -catenin, cyclooxygenase-2, and inducible nitric oxide synthase. In addition, *-catenin* gene mutations were found in colonic adenocarcinomas developed. We also revealed the different susceptibility to AOM/DSS-induced colon carcinogenesis among the four different strains of mice (Balb/c, C3H/HeN, C57BL/6N, and DBA/2N). In the chemoprevention study, dietary administration of nimesulide (COX-2 inhibitor), troglitazone (PPAR ligand), or bezafibrate (PPAR ligand) effectively could suppress the development of colonic epithelial malignancy induced by AOM/DSS in female ICR mice. In the different experiment, we investigated whether DSS exposure can promote the growth of preneoplastic lesions, ACF^{Min} (dysplastic ACF), in the colon of $Apc^{Min/+}$ mice that contain a truncating mutation in the *Apc* gene. Surprisingly, four weeks after the DSS exposure (2% in drinking water for a week) numerous colonic epithelial malignancy developed $Apc^{Min/+}$. Our animal model can be applied for investigating the pathogenesis in colon carcinogenesis of IBD and for identifying xenobiotics with modifying or carcinogenic effects in the colon tumorigenesisk. Also, our series of studies on colitis-related carcinogenesis may provide new insight into the genesis and chemoprevention of cancer development in inflamed colon.