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MOLECULAR BASIS FOR CHEMOPREVENTION OF COLON CANCER

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The number of cancer patients is still on the rise in most developed countries, and the establishment of an effective way to prevent neoplasia is becoming increasingly important. Cancer is a disease of DNA, being associated with multiple genetic alterations. These are generally induced by multiple carcinogenic factors, including xenobiotics and autobiotics, and are also dependent on the genetic background in terms of susceptibility. Clearly, therefore, many approaches to cancer prevention exist. Primary cancer prevention concerns measures to reduce the occurrence of cancer in the general population, for example, by improving life styles, including cessation of smoking. Secondary cancer prevention is detection of cancer as early as possible, and actions to prevent development of malignancies. In addition, chemoprevention is now attracting attention as a means of preventing cancer in high risk groups with chemical substances.

Epidemiological studies have shown that prolonged use of aspirin is associated with a reduced risk of colorectal cancer(1). Consistent with these data, aspirin and related nonsteroidal anti-inflammatory drugs (NSAIDs) have been found to inhibit chemically induced colon cancers in rodents(2). In

addition, clinical trials have demonstrated that one NSAID, sulindac, causes regression of adenomas in patients with familial adenomatous polyposis(3). Conventional NSAIDs such as aspirin, indomethacin and sulindac inhibit both cyclooxygenase-1 (COX-1) and COX-2, but the former is generally more strongly affected. Inhibition of COX-1 by these NSAIDs is a causal factor in their gastrointestinal side-effects, and this is recognized as a serious problem for clinical application as chemopreventive agents in man. Since COX-2 has been suggested to be preferentially involved in inflammation and carcinogenesis, the adverse effects of conventional NSAIDs might be avoided by employing agents, selectively targeting COX-2.

Nimesulide, one such selective inhibitor of COX-2, is used clinically as an anti-inflammatory drug in several European countries. The structure of nimesulide is shown in Fig.1. We recently found that it suppressed the development of intestinal polyps in Min mice when administered at a dose of 400 ppm in their diet for 11 weeks(4). Moreover, nimesulide exerted a suppressive effect on azoxymethane-induced colon cancer development at doses of 200 and 400 ppm in diet in mice(5). Other selective COX-2 inhibitors, including celecoxib and MF tricyclic, have been also demonstrated to reduce intestinal tumor development in rodents(6,7). Thus, selective COX-2 inhibitors are good candidates as chemopreventive agents with low toxicity for human colon cancers. Recently, the chemopreventive potential of nimesulide against the

development of rat superficial urinary bladder carcinomas by *N* butyl *N* (4 hydroxy butyl) nitrosamine was also demonstrated (8).

An important role for the cyclooxygenase pathway of the arachidonic acid cascade has been suggested in colon carcinogenesis. However, the molecular species of prostanoids and receptors involved have yet to be fully elucidated. We examined the development of aberrant crypt foci (ACFs), putative preneoplastic lesions of the colon, in two lines of knockout mice, each deficient in prostaglandin E receptors, EP_1 and EP_3, by treatment with the colon carcinogen, azoxymethane. Formation of ACFs was decreased only in the EP_1-knockout mice to about 60% of the level in wild-type mice. Administration of 250, 500, or 1000 ppm of a novel selective EP_1 antagonist, ONO-8711, in the diet to azoxymethane-treated C57BL/6J mice also resulted in a dose-dependent reduction of ACF formation. Moreover, when Min mice were given 500 ppm ONO-8711 in the diet, the number of intestinal polyps was significantly reduced to 57% of that in the basal diet group. From these results, it is suggested that PGE_2 is involved in colon carcinogenesis to some extent by acting at the EP_1 receptor. Selective EP_1 antagonists may therefore be good candidates as chemopreventive agents for colon cancer (9).

In this paper, the present situation of chemoprevention of cancers in the colon will be described.

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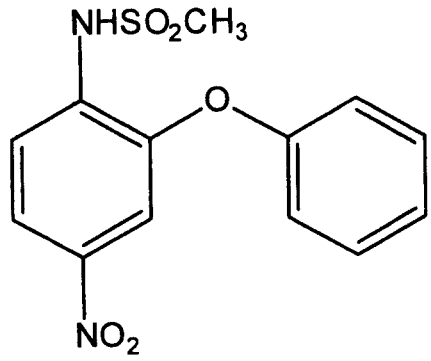

Fig.1. Structure of nimesulide (4-nitro-2-phenoxymethanesulfonanilide).