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Colorectal cancer and non-steroidal anti-inflammatory drugs[1]

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KEY WORDS colonic neoplasms；non-steroidal anti-inflammatory agents；prostaglandin-endoperoxide synthase；prostaglandin；adenoma

ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) can prevent or reduce the occurrence of colorectal cancers. Anti-carcinogenic properties of NSAIDs have been demonstrated in epidemiological studies of humans and experimental animals. In addition，clinical studies of familial adenomatous polyposis and sporadic adenomas have demonstrated that NSAIDs induce regression of colorectal adenomas and prevent formation of these tumors. NSAIDs thus induce early disruption of the adenoma-carcinoma sequence and may mainly suppress subsequent cancer formation at adenoma stage. The mechanism of the anti-carcinogenic effect of these drugs is not known，but results of most studies support that cyclooxygenase-2 (an inducible isoform of prostaglandin synthetase，COX-2) is a major target of NSAIDs in this effect. Recent immunohistochemical studies have revealed that COX-2 is expressed not in tumor cells but in interstitial cells of colonic adenomas. Accordingly，NSAIDs may exhibit anti-carcinogenic property through the inhibition of prostaglandin production by COX-2 expressing interstitial cells. Future research should be focused on the role of prostaglandins in the interaction of tumor cells and interstitial cells in colon carcinogenesis.

INTRODUCTION Since Kudo and Narisawa *et al*[1] showed that indomethacin，a non-steroidal anti-inflammatory drug (NSAID)，suppressed colon carcinogenesis in experimental animals in 1980，various studies have demonstrated that NSAIDs prevent colon cancer. There are three lines of evidence for this. First，cancer prevention studies suggest that there may be a 40－50 % reduction in mortality from colorectal cancer in persons who take aspirin or other NSAIDs on a regular basis[2]. Second，NSAIDs reduce the number and size of colon adenomas[3]. Third，some NSAIDs induce regression of adenomatous polyps in patients with familial adenomatous polyposis (FAP)[4]. Although the efficacy of NSAIDs in preventing colon carcinogenesis has been established，the mechanism by which they do so is still controversial. In the present review，we focused on findings attempting to determine appropriate foci of future research in this area.

NSAIDs reduce the risk of colorectal cancer in humans In 1988，an epidemiological study found a reduction in the incidence of colon cancer in regular users of aspirin[5]. This study showed a 40－50 % reduction in the incidence of colon cancer among regular aspirin users. Most subsequent studies have obtained similar results[5－9]，although a study of elderly Californians reported a moderate increase in colon cancer among aspirin users[10] and another study of healthy male medical doctors taking aspirin found decrease of the incidence of myocardial infarction but no decrease in the relative risk of colon cancer[11].

Thun *et al*[5] reported the largest study of chemoprevention of colon cancer by NSAIDs. Over 600 000 individuals were followed for colon cancer death and aspirin use. The rate of colon cancer death was inversely correlated with aspirin use. The relative risk of fatal colon cancer for those who used aspirin 16 or more times per month was 0.60 in men and 0.58 in women. Further follow-up analysis of the results of this large study demonstrated a decrease in death rate from cancers of the esophagus，stomach，and rectum in addition to that of colon among aspirin users[12].

Considering these reports，regular use of aspirin on long term basis could reduce the risk of colon cancer in human.

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NSAIDs prevent coloncarcinogenesis in animals In 1980 Kudo and Narisawa reported that indomethacin inhibited colon carcinogenesis in rats[1]. Since then several studies have been carried out using animal models which have shown that various NSAIDs including indomethacin, phenylbutazone, aspirin, piroxicam, ketoprofen, and sulindac dramatically reduce the size and number of intestinal tumors[13]. More recently, in ApcMin mice[14] with a germline mutation in Apc, a genetically manipulated animal model of colon cancer, NSAIDs were found to suppress the formation of intestinal tumors[15].

There are at least two isoforms of cyclooxygenase (prostaglandin synthetase, COX) in humans. COX-1 is constitutively expressed in most tissues, whereas COX-2 is induced by cytokines, growth factors, and other agents (Fig 1). Although most NSAIDs suppress both of these isoforms, COX-2-specific inhibitors such as celecoxib (SC-58635)[16], *N*-(2-cyclohexyloxy-4-nitrophenyl) methanesulfonamide (NS-398)[17,18], and nimesulide[19] have also been found to suppress experimental colon carcinogenesis. MF Tricyclic, another COX-2-specific inhibitor, suppressed polyp formation of $Apc^{\Delta 716}$ knockout

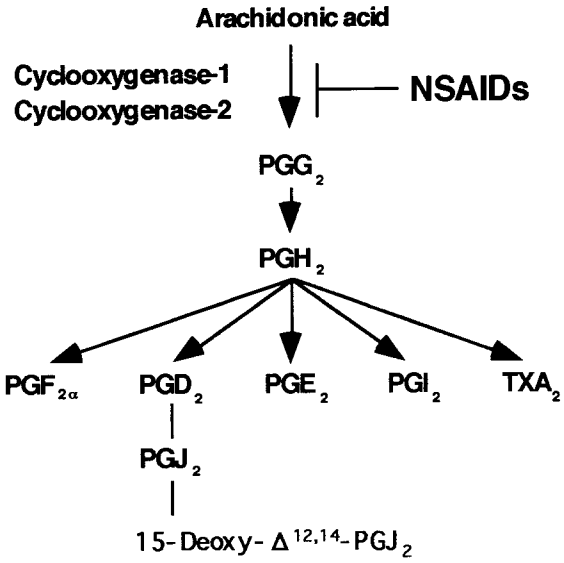

Fig 1. Arachidonic acid cascade. Arachidonic acid is released from membrane phospholipids by phospholipase A_2 and converted by either cyclooxygenase-1 (COX-1) or cyclooxygenase-2 (COX-2) to prostaglandin (PG) G_2 and then to PGH_2. PGH_2 is converted to either PGs or thromboxane (TX) A_2. COX-1 is constitutively expressed in most tissues, while COX-2 is induced by various stimulants. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclooxygenase activity and suppress production of PGs.

mice to a significantly greater extent than sulindac[20].

These experimental findings suggest that NSAIDs including COX-2 specific inhibitors can prevent colon carcinogenesis.

NSAIDs induce regression of adenomas in humans FAP, an autosomal dominant disorder, is characterized by the formation of hundreds of colorectal adenomas and development of colorectal cancer. The genetic mutation responsible for this disease is in the adenomatous polyposis coli (*APC*) gene. Somatic mutations in the *APC* gene have been reported in upto 50 % of sporadic colorectal cancers[21]. Several studies have shown that sulindac, an NSAID, induces regression of colorectal polyp formation in FAP patients[4,22-24]. Waddel and Loughry[22] first reported that use of sulindac induced regression of rectal adenomas in four patients with FAP. Thereafter, several cases were reported regarding resolution of adenomas in FAP patients by sulindac. Giardiello *et al*[4] conducted randomized, double-blinded, placebo-controlled trial in 40 patients with FAP. Patients receiving oral sulindac (300 mg/day) exhibited decreases in number (44 %) and size (35 %) of polyps, while there was no regression of polyps in the placebo group. No patient showed complete resolution of adenomas.

For sporadic adenomas of the colon, conflicting results have been reported. Polyps on the left side of the colon in 7 cases did not regress after a 6-month treatment with sulindac or piroxicam[25]. Hadenheim *et al*[26] performed randomized, double-blinded, placebo-controlled trial in 44 patients with sporadic colonic adenomas. Neither polyp regression nor polyp size differed significantly between the sulindac and control group after 4 months of treatment. However, Matsuhashi *et al*[27] found that 13 of 20 polyps shrank or disappeared after treatment with sulindac (300 mg/day) for four months. One adenoma containing a focal cancer did not respond to treatment. One of the sulindac-treated patients developed rectal cancer 16 months after sulindac treatment[28], suggesting that careful follow-up is required in chemoprevention of colon cancer. These discrepancies between study results have been caused by the small numbers of patients studied. A recent colonoscopy-based case control study by Mandler *et al*[29] showed that NSAID use significantly reduced the incidence of colonic adenomas. The odds ratio in the study was 0.56. They, therefore, concluded that NSAIDs induce early disruption of the adenoma-carcinoma sequence.

Taken together, these findings suggest that treatment

with sulindac causes polyps of FAP patients and some sporadic polyps to regress. The difference in results for sporadic polyps might be associated with the presence of mutation of the APC gene; the reason for these differences requires further investigations. However, these results suggest that NSAIDs may prevent the development of human colon cancer at the adenoma stage.

Is COX-2 a molecular target in the prevention of colon carcinogenesis by NSAIDs? Several studies have shown that COX-2, but not COX-1 mRNA and/or protein expression is elevated in human colon cancers and adenomas, compared to that in normal mucosa[30-32]. Similarly, COX-2 mRNA and protein levels are markedly elevated in adenomas and cancers in carcinogen-induced rats and *Apc*^{Min} mice[33,34]. Further, COX-2 inhibitors suppress the formation of intestinal tumors in these animal models[16-19]. These findings suggest the importance of COX-2 in NSAID-induced prevention of colon cancer. A study using *Apc*$^{\Delta716}$ knockout mice, a model of human FAP, revealed functional evidence of the importance of COX-2 in intestinal polyp formation[20]. The study showed that inactivating the Ptgs 2 (mouse COX-2) gene in *Apc*$^{\Delta716}$ knockout mice or administration of a COX-2-selective inhibitor dramatically reduced the number and size of intestinal polyps. This gives a direct genetic evidence that COX-2 plays a key role in the early stage of intestinal polyp formation.

Where is COX-2 expressed in the adenomacarcinoma sequence of human colon cancer? Although COX-2 is up-regulated in colon cancer, an immunohistochemical study revealed that COX-2 is not diffusely expressed in cancer cells[31]. Additionally, there is no evidence that NSAIDs have any therapeutic effects in advanced colon cancer, while they may induce regression of human colonic adenomas[21-23,27]. Therefore research should be focused on the expression of COX-2 in adenomas, the precursor lesions of human colon cancer.

COX-2 mRNA and/or protein level is elevated in adenomas of both humans and experimental animals[30,33,34]. The location of expression of COX-2 in intestinal adenoma is controversial. Williams *et al*[34] showed immunohistochemically that COX-2 protein was over-expressed in epithelial cells of dysplastic and neoplastic foci in intestinal mucosa of *Apc*^{Min} mice. However, a recent study by Oshima *et al*[20] using *Apc*$^{\Delta716}$ knockout mice yielded interesting findings inconsistent with this study. They showed that COX-2 plays a crucial role in the very early stage of intestinal polyp formation, and that COX-2 expression is limited to interstitial cells. Additionally, Hull *et al*[35] demonstrated that COX-2 protein is located in interstitial cells, mainly macrophages, at the base of and within adenomas of the small and large intestine of *Apc*^{Min} mice. These discrepancies in findings might be due to differences in the specificity of COX-2 antibody or tissue preparation. It will thus be essential to study the localization of COX-2 in human colonic adenoma to sort out the differences in the results of animal studies. Bamba *et al*[36] examined the specificity of anti-human COX-2 antibody and performed immunostaining of human sporadic colon adenomas and cancer. They found that COX-2 was strongly expressed in subepithelial interstitial cells in the surface area of human colonic adenomas. The localization of CD68-positive cells, ie. macrophages, was similar to that of COX-2-positive cells in human colonic adenomas, consistent with the study of *Apc*^{Min} mice by Hull *et al*[35].

These studies suggest that the target of NSAIDs in preventing colon carcinogenesis may be COX-2 expressed in interstitial cells, possibly macrophages of colonic adenomas.

What is the role of COX-2 in colon carcinogenesis? Induction of apoptosis in colon cancer cells by NSAIDs has been proposed as one possible mechanism of suppression of colon cancer by these drugs[37-39]. When COX-2 was overexpressed in rat intestinal epithelial cells, these cells were more resistant to sodium butyrate-induced apoptosis[40]. The resistance of these cells to apoptosis was reversed by NSAIDs. These observations suggested the hypothesis that NSAIDs prevent colon carcinogenesis by inducing apoptosis in colon cancer cells through inhibition of COX-2. Nevertheless, NSAIDs have been shown to induce apoptosis in colon cancer cell lines independent of COX-2 protein expression[41,42]. Therefore, COX-2 may not protect against NSAID-induced apoptosis in colon cancer cell lines. Further, these studies focused mainly on the role of apoptosis in colon cancer cells in the prevention of colon carcinogenesis. As previously mentioned, COX-2 which might be a principal target of NSAIDs is mainly expressed in interstitial cells of intestinal adenomas. Accordingly, these studies have only limited ability to reveal the mechanisms by which NSAIDs prevent colon carcinogenesis.

What are then the roles of COX-2 expressing interstitial cells in colon carcinogenesis? Since COX-2 is mainly expressed in interstitial cells and not in epithelial cells, prostaglandin (PG) produced by these cells may play an important role in colon carcinogenesis (Fig 2).

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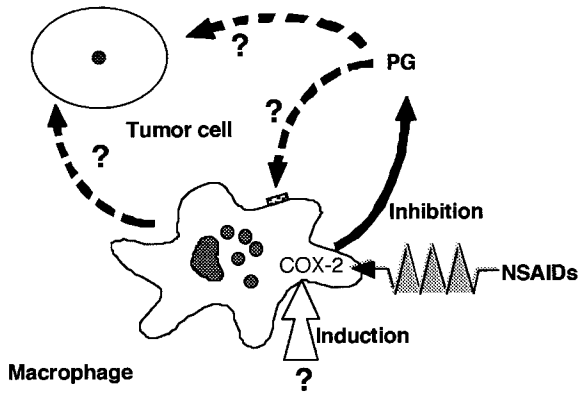

Fig 2. Possible roles of COX-2 expressing macrophages in colon carcinogenesis. PG；prostaglandin，NSAIDs；non-steroidal anti-inflammatory drugs，COX；cyclooxygenase.

COX-2-derived PG may stimulate cancer cell proliferation[42] and inhibit apoptosis in tumor epithelial cells[43]. Macrophage-derived PGE_2 also appears to be responsible for immunosuppression[44]. Alternatively，induction of growth factors，which play important roles in cancer progression[45]，by PG might be involved in colon carcinogenesis，since PG is a potent inducer of growth factors in other interstitial cells[46,47]. Moreover，in our previous studies we found that HGF production was dramatically increased by COX-2-expressing human colonic fibroblasts through a PG-mediated pathway，and that indomethacin，an NSAID，suppressed PG-mediated HGF production in these cells[48]. The great interest in tumor-stromal interaction thus stems from the fact that COX-2 is expressed in macrophages of human colonic adenomas，although it remains unclear what induces COX-2 in macrophages and how macrophages expressing higher levels of COX-2 affect colon carcinogenesis. Further studies should be focused on these lines.

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结肠直肠癌和非甾类消炎药[1]

关键词 结肠肿瘤；非甾类消炎药；前列腺素内过氧化物合酶；前列腺素；腺瘤

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