

**Editorial**

**Cyclooxygenase-2 and Hepatocellular Carcinoma: Is It a Target for Prevention?**

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Bae et al. (1) report in this issue of *Clinical Cancer Research* that COX-2 is expressed in a subset of human hepatocellular carcinomas with higher levels in more well-differentiated carcinomas. COX-2 belongs to a class of genes referred to as “immediate early” or “early growth response” genes (2). It has been known for >10 years that this set of genes is highly inducible in hepatocytes after partial hepatectomy (3); therefore, it is not surprising that COX-2 levels are increased in neoplastic liver cells.

For over a decade, we have known that there is a significant reduction in risk for colorectal cancer in persons who take nonsteroidal anti-inflammatory drugs (cyclooxygenase inhibitors) on a regular basis (4). COX-2 levels were first reported to be elevated in human colon carcinomas in 1994 (5). After this initial report, several groups confirmed that COX-2 levels are increased in most colorectal cancers (6–8). Now there is a significant amount of evidence to support the hypothesis that COX-2 has proneoplastic effects in intestinal cancer and to indicate that inhibition of COX-2 activity results in a decrease in tumor growth (9). Overexpression of COX-2 in intestinal epithelial cells leads to a proneoplastic phenotype in which there is a resistance to undergo programmed cell death (10), an increase in expression of matrix metalloproteinase enzymes (11), and alterations in colony morphology (11). In preclinical studies of intestinal cancer, lack of the COX-2 gene results in a marked decrease in tumor burden (12), treatment with selective COX-2 inhibitors results in a decrease in tumor size and multiplicity (13–16), and human studies in patients with a genetic predisposition for colorectal cancer indicate that treatment with the selective COX-2 inhibitor, celecoxib, for 6 months results in a 30% reduction in adenoma size and number (17). Other types of solid malignancies have also been reported to have elevated levels of COX-2, such as skin (18), lung (19), breast (20), prostate (21), bladder (22), and uterus (23). Work is under way to determine whether COX-2 selective inhibitors have a role in the treatment and/or prevention of these other types of cancer.

The role of COX-2 in hepatocellular carcinogenesis is less clear. It has been documented that colorectal cancer, metastatic to the liver, expresses COX-2 (24). Also, previous reports indicate that COX-2 levels are elevated in some hepatocellular carcinomas (25–27). The current study by Bae et al. (1) reports that there is a significant correlation between the presence of COX-2 and the state of differentiation. Bae et al. (1) also show that there was no relationship between the level of COX-2 expression and α-fetoprotein, tumor size, the presence of portal vein thrombosis, and metastatic spread. Additionally, treatment of cultured HCC cells with a selective COX-2 inhibitor (NS-398) stimulated apoptosis. These effects have been reported by others in studies of cultured epithelial cells; therefore, the results are not surprising (15, 28, 29). However, the concentration of drug required to achieve a significant stimulation of apoptosis *in vitro* is much higher than that required to inhibit COX-2 activity. Therefore, these proapoptotic effects are not likely to be related to inhibition of COX-2, as reported previously (15). Of interest, others have shown that treatment of intestinal epithelial cells with NS-398 induces the expression of a proapoptotic gene, Par-4 (28). It would be of interest to determine whether this gene is also up-regulated in hepatocellular carcinoma cells after treatment with NS-398. If so, this could explain one of the underlying mechanisms responsible for increased programmed cell death after treatment with a selective COX-2 inhibitor.

Hepatocellular carcinoma is a leading cause of cancer deaths worldwide. Oftentimes the disease develops to an advanced stage before it is detected clinically. If an effective chemopreventive option could be developed, then persons at high risk for hepatocellular carcinoma would benefit greatly. It is too early to tell whether selective COX-2 inhibitors will have a role in this disease. However, the work by Bae et al. (1) reported here is intriguing and demonstrates that these issues should be explored further. Important questions remain to be answered. Why is COX-2 expressed mainly in well-differentiated hepatocellular carcinomas, and what phenotypic changes result from forced expression of COX-2 in the normal hepatocyte?

**References**


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