**Letter to the Editor**


Recently, Kondo et al. (1) reported that the level of COX-1/2 increased from normal liver to chronic hepatitis to cirrhosis. An increase in COX-2 expression in the nontumor tissues was significantly associated with relapse of HCC, which is of great interest from a clinical point of view. They suggested that the presence of active inflammation, which is highly correlated with COX-2 expression, was involved in the development of tumor relapse. On the other hand, a significant association was observed between COX-2 expression and the histological grade of HCC. Well- and moderately differentiated HCCs expressed COX-2 more strongly than poorly differentiated HCC. Taken together, these findings indicate that COX-2 may be associated with the early process of the progression of HCCs. COX-2 is a rate-limiting enzyme in the conversion of AA to prostaglandins (PGs) and other eicosanoids. AA is largely derived by biotransformation from an essential fatty acid, LA. Therefore, such a sharp fluctuation in the COX-2 enzyme activity (1) might affect the hepatic tissue fatty acid composition, especially the amounts of AA and LA. We recently determined the fatty acid composition of both HCC and nontumor tissues that had been surgically resected in the Department of Surgery II, Kyushu University. Eighteen HCC specimens with adjacent nontumor tissue, involving 10 cases of chronic viral hepatitis and 8 cases of cirrhosis, and 8 surgically resected, histologically normal liver tissue were used. Each HCC was histologically graded into one of three categories: well differentiated, moderately differentiated, and poorly differentiated. Well- and moderately differentiated HCCs expressed COX-2 more strongly than poorly differentiated HCC. Taken together, these findings indicate that COX-2 may be associated with the early process of the progression of HCCs. COX-2 is a rate-limiting enzyme in the conversion of AA to prostaglandins (PGs) and other eicosanoids. AA is largely derived by biotransformation from an essential fatty acid, LA. Therefore, such a sharp fluctuation in the COX-2 enzyme activity (1) might affect the hepatic tissue fatty acid composition, especially the amounts of AA and LA. We recently determined the fatty acid composition of both HCC and nontumor tissues that had been surgically resected in the Department of Surgery II, Kyushu University. Eighteen HCC specimens with adjacent nontumor tissue, involving 10 cases of chronic viral hepatitis and 8 cases of cirrhosis, and 8 surgically resected, histologically normal liver tissue were used. Each HCC was histologically graded into one of three categories: well differentiated, moderately differentiated, and poorly differentiated, according to the criteria proposed by the Liver Cancer Study Group of Japan (2). The hepatic tissue specimens were extracted according to the method of Folch et al. (3). The tissue fatty acids were converted to methyl esters and analyzed by gas chromatography on a SUPELCOWAX-10 fused silica capillary column (30-m × 0.53-mm × 1.0-μm film thickness).

The content of both the LA and the AA (Fig. 1, A and B, respectively) varied in a manner quite similar to that of COX-2 expression (1). The lowest amount of AA was detected in the normal liver, and the amount of AA increased from normal liver to chronic hepatitis to cirrhosis (Fig. 1B). These findings reinforce the suggestion that the amount of AA may also be associated with the early stages of hepatic carcinogenesis. On the other hand, well-differentiated HCC contained the highest LA content among the three histological grades of HCC, and the amount of LA content decreased when the HCC was graded more poorly differentiated (Fig. 1A). This is the first demonstration that the tumor dedifferentiation of human HCC is correlated with the tissue fatty acid composition.

The reason for the increased amount of AA in chronic hepatitis and cirrhosis remains to be established. However, the increase in the AA content may aggravate the active inflammation because AA is the main substrate for the COX-2 pathway to produce proinflammatory eicosanoids. Several recent studies (4) have shown overexpression of COX-2 to be related to a poorer prognosis in cancer patients, thus suggesting that the metabolites of AA, such as PGE2, play an important role in tumorigenesis. To ameliorate the active inflammation and subsequently to inhibit tumor carcinogenesis, reductions in both the COX-2 activity and the tissue AA content seem to be desirable. Both nonsteroidal anti-inflammatory drugs and selective COX-2 inhibitors suppress inflammation, at least partially, by inhibiting the COX-2 activity. It has recently been reported that dietary fats also modulate the COX-2 expression (5, 6). Dietary fish oil rich in n-3 PUFAs inhibited COX-2 expression and suppressed colon tumor development in animals (5). Furthermore, it is well known that the dietary consumption of n-3 PUFAs decreases the

---

**Fig. 1** The amounts of LA (A) and AA (B) in three different nontumorous hepatic tissue specimens and in three different histological grades of HCC tissue. CVH, chronic viral hepatitis; LC, liver cirrhosis; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.

---

1 The abbreviations used are: COX, cyclooxygenase; HCC, hepatocellular carcinoma; AA, arachidonic acid; LA, linolenic acid; PUFA, polyunsaturated fatty acid.
2 To whom requests for reprints should be addressed, at The Department of Surgery, Medical Institute of Bioregulation, Kyushu University, Beppu 874-0838, Japan. Phone: 81-977-27-1650; Fax: 81-977-27-1651; E-mail: tohru@tsurumi.beppu.kyushu-u.ac.jp.

Received 4/18/00; revised 9/6/00; accepted 9/6/00.
tissue amount of AA (7). A number of studies have demonstrated that dietary n-6 PUFA such as LA promote tumor carcinogenesis, whereas n-3 PUFAs are inhibitory. Although the number of patients included in this study was relatively small, it may be valuable to examine whether dietary n-3 PUFA or combination therapy with a pharmacological inhibition of COX-2 activity suppress inflammation and thus lead to better prognosis for patients with carcinomas such as HCC.

Tohru Utsunomiya
Mitsuo Shimada
Tatsuya Rikimaru
Keizo Sugimachi
Department of Surgery II
Kyushu University
Faculty of Medicine
Fukuoka 812
Japan
Ken-Ichi Ohkura
Shihoko Kaku
Koji Yamada
Department of Food Science and Technology
Kyushu University
Faculty of Agriculture
Fukuoka 812
Japan
Ken-Ichi Taguchi
Department of Pathology II
Faculty of Medicine
Fukuoka 812
Japan

References

Tohru Utsunomiya, Mitsuo Shimada, Tatsuya Rikimaru, et al.


Updated version Access the most recent version of this article at: http://clincancerres.aacrjournals.org/content/6/12/4965

Cited articles This article cites 6 articles, 4 of which you can access for free at: http://clincancerres.aacrjournals.org/content/6/12/4965.full#ref-list-1

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.