Cyclooxygenase-2: A Potential Target in Human Cancer

Jong-Ho Won, M.D.

Division of Hematology-Oncology and Institute for Clinical Molecular Biology Research, Soon Chun Hyang University College of Medicine, Seoul, Korea

Cyclooxygenase (COX) inhibitors are being developed as potential agents for the prevention and treatment of cancer after a century of their widespread use for inflammation, fever and pain. Beginning in the late 1970s, researchers noted elevated concentrations of prostaglandins in neoplastic lesions, and this suggested a role for arachidonic acid metabolites in tumorigenesis. Multiple lines of evidence - *in vitro*, *in vivo*, observational and clinical - have now confirmed that COX inhibitors reduce prostaglandin production and the risk of colorectal, skin, and other neoplasias (1,2). The recent development of selective inhibitors for the inducible form of COX, COX-2, represents another important advance. Most importantly, selective COX-2 inhibitors cause fewer serious adverse effects than traditional NSAIDs (3,4). The improved safety profile of selective COX-2 inhibitors makes it realistic to consider their long-term use in individuals who are at low to moderate risk for cancer.

COX, the enzyme that catalyses the conversion of arachidonic acid to prostaglandins, is involved in several physiological and pathogenetic pathways (5). Two isoforms are known. COX-1 is constitutively expressed in most tissues and produces prostaglandins involved in maintenance of the gastric mucosa, regulation of renal blood flow, and platelet aggregation (6). The inducible form, COX-2, is expressed in inflamed and neoplastic tissues and is induced by proinflammatory and mitogenic stimuli, such as growth factors (epidermal growth factor [EGF], vascular endothelial growth factor [VEGF], fibroblast growth factor [FGF]) and cytokines (tumor necrosis factor α [TNF α], interleukins 1 α and 1 β). Certain mutations can also upregulate COX-2 (eg, v-src, v-Ha-ras, HER-2/neu, and Wnt). The presence of *cis*-acting elements in the 5'-flanking region of the COX-2 gene, including nuclear factor κ B (NF κ B), nuclear factor-interleukin 6 (NF-IL6), and cAMP response element (CRE) sites, and the increased stability of COX-2 mRNA may upregulate COX-2 overexpression (7 ~ 10). COX-2 is expressed in macrophages, synoviocytes, fibroblasts, osteoblasts, tumor cells, and "activated" endothelial cells (8,11). Recent research has suggested a role for COX-2 in neoplasia, including hyperproliferation, transformation, tumor growth, invasion, and metastasis (11).

A number of studies have shown the overexpression of

COX-2 in solid malignancies including breast, pancreas, prostate, and colon (5,6,12). Immunohistochemical studies have shown COX-2 overexpression in premalignant lesions such as oral leucoplakia, actinic keratosis, prostatic intraepithelial neoplasia, and carcinoma-in-situ of the bladder and breast. COX-2 is also upregulated in several invasive tumor types. In general, COX-2 expression is higher in the well to moderately differentiated tumors, and in metastases. A significant relation between the overexpression of COX-2 and the survival of patients with breast, colon, gastric, and lung cancers has been reported in retrospective studies (11).

In this issue of the journal, Ahn et al. (13) reported a series of studies with COX-2 expression in human breast carcinoma. The authors analyzed the tissue samples from 205 patients surgically resected for breast cancer. The samples were immunohistochemically stained with antibodies to COX-2, *c-erb*-B2, and CD34 and then compared for clinicopathological characteristics and survival. COX-2 expression was detected in 57.6% of the cases. COX-2 expression was significantly higher in *c-erb*-B2 positive tumors and could also be positively correlated with the microvessel count, but not with any other clinicopathological characteristics, including tumor size, involved axillary lymph nodes, estrogen or progesterone receptor status, and survival. At least 8 different immunohistochemical studies have investigated the expression of COX-2 in a total of 2392 primary breast carcinomas, of which 40% were found to be COX-2 positive. The overexpression of COX-2 was associated with known indicators of poor prognosis, such as lymph node metastasis, poor differentiation and large tumor size. Four studies have found that the overexpression of COX-2 was linked to poor prognosis for breast cancer (14). There are conflicting data regarding the frequency of COX-2 expression and relation between the overexpression of COX-2 and survival in breast cancers. These discrepant observations can be reconciled by consideration of the following. First, the different methods to detect COX-2 may reflect the sensitivity of the results. The second important caveat is that COX-2 expression may be predominantly associated with certain subsets of human breast cancers (15). Interestingly, this study indicated that COX-2 expression was significantly higher in *c-erb*-B2 positive tumors and co-expression of COX-2 and *c-erb*-B2 showed the tendency for poorer disease free survival in breast cancer patients. These results can augment the growing evidence that the COX-2 and *c-erb*-B2 pathways may be interconnected.

Since the discovery of the COX-2 gene about 10 years ago, enormous research progress has been made. Although there is

Correspondence: Jong Ho Won, Division of Hematology-Oncology and Institute for Clinical Molecular Biology Research, Soon Chun Hyang University College of Medicine, 657 Hannam-dong, Yongsan-gu, Seoul 140-743, Korea. (Tel) 02-709-9203, (Fax) 02-709-9200, (E-mail) jhwon@hosp.sch.ac.kr

much compelling data to support the link between the overexpression of COX-2 and carcinogenesis, many unanswered questions yet remain. Pharmacodynamic studies have shown several mechanisms for the anticancer effects of COX-2 inhibitor: blocking angiogenesis, promotion of apoptosis, modulation of immune surveillance, and inhibition of tumor cell invasion. However, the relative importance of each of these effects for carcinogenesis is somewhat uncertain. We do not yet know much about the optimal timing of COX-2 inhibition for cancer. It is probable that these drugs will be most effective during the early stages for the development of tumors. In addition to the colorectal adenoma prevention studies, the clinical trials for patients at an increased risk of cancers of the esophagus, oral cavity, skin, and bladder will provide important insights. Another unresolved issue concerns the combination of COX-2 inhibitors with other therapeutic agents, and also with novel molecular targeting compounds. Obviously, a strategy that targets multiple pathways simultaneously may be critical for improving not only the efficacy of single agent therapy, but also for a combined modality therapy in the prevention and treatment of cancer. Data published in this issue of the Journal shows the possibility of the combination of COX-2 inhibitors and trastuzumab, a monoclonal antibody against *c-erb*-B2 in breast cancer (13).

In summary, COX-2 inhibitors present many important advantages: they are orally active, have moderate side effects, and have few medical contraindications. The antitumor effects of COX-2 inhibitors are enhanced in combination with conventional antitumor agents, radiotherapy, and molecular targeting compounds. These findings might well expand the therapeutic potential of COX-2 inhibitors, and especially in chemoprevention and adjuvant settings.

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