Kenji Ogawa, Kazuhiko Yoshimatsu

Cyclooxygenase II
– A Role in Gastric Cancer Treatment

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Abstract
Recent studies have demonstrated that increased amount of prostaglandin E₂ (PGE₂) produced by overexpression of cyclooxygenase-2 (COX-2)/microsomal PGE synthase-1 (mPGES-1) is involved in tumor proliferation. Furthermore, relationships with epidermal growth factor (EGF)/mitogen activated protein (MAP) kinase signal pathway related to cell proliferation and Akt/protein kinase B (PKB) related to resistance of apoptosis are being clarified. Association of COX-2 with gastric cancer has not been established as clearly as in colon cancer. However, increased expression of COX-2 in gastric cancer was confirmed, and in cell culture or animal models, influence of COX-2 on tumor proliferation was indicated. Thus, the usefulness of COX-2 inhibitor in treatment has been demonstrated. However, in precancerous lesions of gastric cancer, COX-2 expression is controversial and the usefulness of COX-2 inhibitor has not been demonstrated. Further studies about COX-2 and gastric cancer including clinical trials are needed, and also more studies should be performed about other PGE₂ related enzymes as well as COX-2 (Adv Clin Exp Med 2007, 16, 3, 347–352).

Key words: cyclooxygenase-2 (COX-2), microsomal prostaglandin E synthase-1 (mPGES-1), gastric cancer, chemoprevention, COX-2 inhibitor.

Since epidemiological studies reported that long-term users of non-steroidal anti-inflammatory drugs (NSAIDs) would develop colon and gastric cancer less frequently [1, 2], a large amount of studies on a relationship between a target enzyme of NSAIDs, cyclooxygenase (COX) or prostaglandin (PG, especially PGE₂) and cancer development has been reported. Especially for COX-2 whose expression is induced in inflammation and tumor, the expression status in various types of carcinoma was established [3], and it attracts a lot of attention as a target molecule for chemoprevention and treatment of cancer. This review describes a role of COX-2 in gastric cancer and the potential clinical use of a COX-2 inhibitor.

Enhanced PGE₂ Production and Its Role in Tumor Tissue

Production of some PGs particularly PGE₂ increases in gastrointestinal cancer, especially colon cancer. Particularly, PGE₂ production enhances [4], PGE₂ is converted from a membrane phospholipid to arachidonate under cytosolic phospholipase A₂ (cPLA₂) effect, as are other PGs. Subsequently, it is converted to PGH₂ by COX-1 or COX-2, and further converted to PGE₂ by prostaglandin E synthase (PGES). Among the kinds of PGES that are already discovered, analyses of microsomal PGES-1 (mPGES-1) which is inducible type and cytosolic PGES (cPGES) which constitutively express are reported. Interestingly, cPGES and COX-1, mPGES-1 and COX-2 are functionally coupled [5, 6]. In tumor tissue, PGH₂ produced excessively by COX-2 could be efficiently converted to PGE₂ by mPGES-1 (Fig. 1), and overexpression of COX-2 and mPGES-1 in various cancers has been reported (Tables 1, 2) [7–18].

Regarding carcinogenesis, although the effect by genetic change has been analyzed, the effect of PGE₂ produced in tumor tissue (tumor and stroma) is still unknown on tumor cell proliferation. In
a study using COX-2 knockout mice, COX-2 expression was involved in microvessel density in tumor tissue, and this resulted in decreased tumor proliferation [19]. It was also shown that COX-2 and mPGES-1-derived PGE2 were associated with angiogenesis via EP2 [20, 21].

On the other hand, relationship between PGE2 and epidermal growth factor (EGF)-mitogen activated protein (MAP) kinase signal pathway related to tumor proliferation has been recently reported. PGE2 promotes release of transforming growth factor-α (TGF-α), a ligand of EGF receptor (EGFR), and activates extracellular regulated MAP kinase2 (ERK2). After oral administration of PGE2 to rats, phosphorylation of EGFR and ERK2 in mucosal epithelium was observed [22].

Cultured models confirmed that high and concomitant expression of COX-2 and mPGES-1 increased cell proliferation activity and led to morphologic change, and showed tumorigenecity in

Table 1. COX-2 expression in premalignant and malignant tissue

<table>
<thead>
<tr>
<th>Organ</th>
<th>Premalignancy</th>
<th>Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>leukoplakia</td>
<td>squamous cell carcinoma</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Barrett’s esophagus</td>
<td>adenocarcinoma</td>
</tr>
<tr>
<td>Stomach</td>
<td>metaplasia</td>
<td>squamous cell carcinoma</td>
</tr>
<tr>
<td>Colon</td>
<td>adenoma</td>
<td>adenocarcinoma</td>
</tr>
<tr>
<td>Liver</td>
<td>chronic hepatitis</td>
<td>adenosquamous carcinoma</td>
</tr>
<tr>
<td>Biliary System</td>
<td>bile duct hyperplasia</td>
<td>hepatocellular carcinoma</td>
</tr>
<tr>
<td>Pancreas</td>
<td>pancreatic intraepithelial neoplasia</td>
<td>cholangiocarcinoma</td>
</tr>
<tr>
<td>Breast</td>
<td>ductal carcinoma-in-situ</td>
<td>adenocarcinoma</td>
</tr>
<tr>
<td>Lung</td>
<td>atypical adenomatous hyperplasia</td>
<td>adenocarcinoma</td>
</tr>
<tr>
<td>Bladder</td>
<td>dysplasia</td>
<td>squamous cell carcinoma</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>cervical intraepithelial neoplasia</td>
<td>adenocarcinoma of cervix</td>
</tr>
<tr>
<td>Penis</td>
<td>penile intraepithelial neoplasia</td>
<td>squamous cell carcinoma</td>
</tr>
<tr>
<td>Skin</td>
<td>actinic keratoses</td>
<td>squamous cell carcinoma</td>
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</tbody>
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Table 2. mPGES-1 expression in premalignant and malignant tissue

<table>
<thead>
<tr>
<th>Organ</th>
<th>Premalignancy</th>
<th>Malignancy</th>
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<tbody>
<tr>
<td>Head and neck</td>
<td>leukoplakia</td>
<td>squamous cell carcinoma</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Barrett’s esophagus</td>
<td>intestinal type adenocarcinoma</td>
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<tr>
<td>Stomach</td>
<td>adenoma</td>
<td>adenosquamous carcinoma</td>
</tr>
<tr>
<td>Colon</td>
<td>adenoma</td>
<td>adenocarcinoma</td>
</tr>
<tr>
<td>Biliary System</td>
<td>ductal carcinoma-in-situ</td>
<td>adenocarcinoma of gall bladder</td>
</tr>
<tr>
<td>Breast</td>
<td>tobacco smoke exposed</td>
<td>adenocarcinoma</td>
</tr>
<tr>
<td>Lung</td>
<td>epithelial fibroblast</td>
<td>adenocarcinoma</td>
</tr>
<tr>
<td>Bladder (rat)</td>
<td>papilloma</td>
<td>adenocarcinoma</td>
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<tr>
<td>Gynecologic</td>
<td>penile intraepithelial neoplasia</td>
<td>adenocarcinoma of cervix</td>
</tr>
<tr>
<td>Penis</td>
<td>penile intraepithelial neoplasia</td>
<td>squamous cell carcinoma</td>
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</table>
nude mice [23]. In transgenic mice in which these genes expressed in gastric mucosa, PGE₂ production was enhanced and abnormal differentiation was observed. At 48 weeks old, hyperplastic tumor without dysplasia was also observed [24]. PGE₂ produced excessively by COX-2 and mPGES-1 is very important for in vivo cell proliferation but insufficient for malignant change. A study using similar models showed that Wnt signal, that played an important role in development of colon cancer, had importance also in development of gastric cancer [25].

**COX-2 Expression in Gastric Cancer**

Recent epidemiological investigation reported that there were few mortalities from gastric cancer in aspirin users [26]. And also described that occurrence of gastric cancer decreased in long-term users of NSAIDs [27].

In gastric cancer as in various other cancers, COX-2 overexpressed [28]. The expression of COX-2 was mainly observed in tumor cells, but expression was also observed in stromal cells and macrophages. The COX-2 expression in gastric precancerous lesion was shown in intestinal metaplasia and dysplasia [29, 30]. A comparison study between before and after Helicobacter pylori (H. pylori) eradication reported that COX-2 expression level decreased in epithelium and stroma after eradication, but that there was no change in intestinal metaplasia [31]. In the progression process of gastric mucosa to dysplasia and cancer, increased expression of COX-2 was observed [32]. In gastric adenoma, up-regulated COX-2 protein was detected in stromal cells [33]. This indicates that COX-2-derived PGE₂ is associated with cell proliferation as in COX-2/mPGES-1 transgenic mice mentioned above. Thus, further studies are needed to elucidate how COX-2 may be associated with genetic change in carcinogenesis in stomach that has not been clarified as well as in colon cancer. Recent reports confirmed p53 accumulation in all adenoma patients examined and indicated that 50% of the patients showed overexpression of COX-2. The same results were also found in gastric cancer; they demonstrated that the process of cancer development is different between gastric and colon cancer [34].

Regarding the clinicopathological findings and COX-2 expression in gastric cancer, various reports are provided. No relationship between COX-2 expression and age or gender was reported. The lower expression of COX-2 in cardiac gastric cancer was reported [35], and this supports the data indicating that epidemiologically aspirin-use could not prevent cancer related death in patients with cardiac cancer. However, there are no other reports on difference in COX-2 expression by location thereafter. As for histological type and COX-2 expression, some reports showed a higher COX-2 expression in intestinal type [36–38], but no difference in another report [39]. Similarly, there is no consensus on the relationship between COX-2 expression and tumor depth, venous or lymphatic invasion, metastasis or stage [40–42]. Since most studies on association with prognosis were based on univariate analysis [43], further investigation using a large amount of clinical data such as meta-analysis are needed to clarify whether it can be an independent prognostic factor.

**Potential of COX-2 Inhibitor in Gastric Cancer Treatment**

Using culture model, a COX-2 inhibitor, nimesulide inhibited proliferation of MKN-45 cells, and telomerasc activity through blocking Akt/protein kinase B (PKB) pathway [44]. In SGC7901 cells, genetic or pharmacological inhibition of COX-2 reduced PGE₂ production. This resulted that migration and tube formation of HUVEC and in vivo angiogenesis were also inhibited [45]. It was indicated that inhibited COX-2 prevented neovascularization related to gastric cancer. In xenograft model using MKN-45 and nude mice, another COX-2 inhibitor, NS398, inhibited tumor growth. NS398 administration decreased PGE₂ and PGF₁α levels in the tumor tissue. In tumor cells, decreased bromodeoxyuridine (BrdU) index and increased apoptotic index were observed [46]. In other study using OCUM-2M, scirrhous type gastric cancer cell, and NF-21, gastric fibroblast, JTE-522, a COX-2 inhibitor, inhibited NF-21 proliferation but did not inhibit OCUM-2M proliferation. However, in xenograft model, the COX-2 inhibitor did not show a growth inhibition against OCUM-2M alone inoculated tumor but in contrast decreased the size of tumor inoculated with both of OCUM-2M and NF-21. In the tumor tissue, inhibited Ki67 and increased apoptosis were observed, and keratinocyte growth factor (KGF) production from NF-21 was decreased. In scirrhous type gastric cancer, it was demonstrated that COX-2 inhibitor controlled relevance to stromal cell proliferation [47]. In chemical carcinogenesis rat model, the COX-2 inhibitor, cerecoxib also reduced the incidence of gastric cancer and tumor volume [48].

Some observations have been reported on clin-
ical effects of COX-2 inhibitor from the view of gastric cancer prevention. Although H. pylori carriers showed a high level of PGE₂ in gastric mucosa, their PGE₂ level, gastritis score and proliferation indices were not improved after 2-week administration of 25 mg, b.i.d. rofecoxib, a COX-2 inhibitor [49]. From another observation of rofecoxib administration for 2 years, there was no difference in regression of intestinal metaplasia considered to be a precancerous lesion of gastric cancer, and COX-2 inhibitor could not return intestinal metaplasia of gastric mucosa to normal [50]. From these results, gastric cancer prevention should now be focused on H. pylori eradication. However, serum interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), progastrin and gastrin level were decreased in observation before and after administration of 25 mg, b.i.d. rofecoxib for 2 weeks in gastric cancer patients. In addition, the expression level of BAX and caspase-3 increased, and the expression level of Bcl-2 and survivin decreased [51]. From these data, the above animal experiments and in vitro results, it is expected that a COX-2 inhibitor could be useful for gastric cancer treatment, and a large clinical trial must be needed.

Conclusion and Further Directions

Considering the relationship of COX-2 in development of gastric cancer, the effect of COX-2 inhibitor in gastric cancer treatment could be hopeful. However, there are not only results showing prospective effect but also various concerns. Also in results of large scale clinical trial of COX-2 inhibitor administration for patients with colon polyps including familial adenomatous polyp, increase in cardiovascular events, adverse effects of COX-2 inhibitor, were reported [52–54], and careful attention will be needed to ensure the safety of long-term use. It is expected that further investigation will be performed into what relationship exists between gastric cancer and regulation of mPGES-1 that draws attention in colon cancer [7], or 15-prostaglandin dehydrogenase (15-PGDH), a catabolic enzyme of PGE₂ (Fig. 1) [55, 56]. Besides, we hope the studies in the future that the control of these enzymes can prevent or treat gastric cancer.

References


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